NATIONAL INSTITUTES OF HEALTH

Office of the Director

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 2004 House Appropriations Committee Report Language (H. Rpt 108-188)

Item

Balance in the research portfolio – The Committee reiterates its longstanding view that NIH should distribute funding on the basis of scientific opportunity. The Committee urges the Director and the Administration to continue to resist pressures to earmark, set aside and otherwise politicize these resources. To enhance NIH's flexibility to allocate funding based on scientific opportunity, the Committee has attempted to minimize the amount of direction provided in the report accompanying the bill. For example, there are no directives to fund particular research mechanisms, such as centers or requests for applications, or specific amounts of funding for particular diseases. (p. 55)

Action taken or to be taken

NIH will continue to strive to maintain excellence and balance in its research portfolio. To this end, the Agency makes every effort to address multiple public health needs, capitalize~~s~~ on promising scientific opportunities, and fund~~s~~ the most meritorious research proposals. At the same time, the Agency works to maintain~~s~~ a diversified portfolio of projects to assure progress in multiple areas; it also continues to invest in the training of new investigators and in research equipment and facilities.

In setting research priorities, the NIH seeks the best information and judgment available from tens of thousands of people with diverse experience and expertise. These include investigators, who submit proposals and serve on technical review committees and on various ad hoc workshops and advisory committees; clinicians and public health and health services experts; patient advocacy groups and representatives of the general public; as well as the Directors and scientific program officers in each Institute or Center.

NIH sets priorities based on our collective assessment of how best to reduce the burden associated with specific conditions and by determining how best to capitalize on scientific opportunities. Because research is an inherently dynamic process, so is NIH priority setting. They both develop and adjust to new opportunities. Thus, the distribution of funding for any year is but a snapshot of an evolving process. The relationship between scientific opportunities, burden of illness, and disease-specific funding is multifaceted and not always straightforward or linear.

Once an emerging problem is identified, the amount of disease-specific funding is largely determined by the state of the science. If previous basic research or related disease-specific research suggest promising hypotheses to explore, more disease-specific research, development

and clinical evaluation may be proposed and, ultimately, funded. The relatively rapid advance of research on HIV/AIDS was built on extensive knowledge of retro viruses and the immune system is a striking example of capitalizing on findings from previous research.

If more gaps in knowledge than opportunities are identified, the most productive next step may be to initiate more basic research until new findings lead to new hypotheses. We must continually evaluate what is known, what is not known, and what we need to know to solve the problem before us – identifying knowledge gaps, and proposing new research with the goal of developing solutions to health problems

The amount of NIH funding identified (coded) with a particular disease incompletely indicates the attention paid to that condition. Disease-specific funding fails to reflect the likely benefits of basic research or research coded to other conditions. New scientific opportunities often flow from NIH-sponsored research on broad scientific themes, such as genome projects, development of instrumentation, training in clinical research, or developments in basic science. Historically, support of these arenas of research yielded insights and capacity to stimulate research to address specific diseases.

Assessing the burden associated with a specific disease is also complex. Burden includes more than a count of the number of deaths during a single year. In assessing the burden associated with a specific disorder, the NIH must also consider the incidence, severity, and economic costs of a disease. Absent these considerations, we would never study, chronic, non-life threatening conditions such as blindness, deafness, or arthritis. For priority setting purposes,-measures of burden are used to identify trends, rather than to rank different conditions. Is there an emerging problem? Will it grow in the future? Has there been any progress in preventing a disease or managing a condition?

The priority setting process at NIH, both at the level of the NIH Director and the ICs, functions cooperatively in an effort to fulfill NIH's mission to improve human health through research. ICs frequently collaborate on or jointly fund projects of mutual interest, and as such, many other diseases under study at the NIH require the input of more than one IC. The NIH Director has a unique overview of the entire NIH and influences the Institutes to focus on matters of importance to them all. In addition, program offices in the Office of the Director are also responsible for enhancing some of the cross-Institute coordination of research on disease prevention, rare diseases, women's health, AIDS, and behavioral and social sciences.

The NIH Roadmap represents a new mode of trans-NIH collaboration, and it involved the continued participation of each IC in an effort to reshape the biomedical research agenda. The NIH Roadmap focuses on efforts that the NIH as a whole must address to make the biggest impact on the progress of medical research. Further information about the NIH Roadmap can be found at: http://nihroadmap.nih.gov. In addition to exemplifying a trans-NIH planning and implementation process, NIH Roadmap initiatives will be unique in how they will be funded. All ICs will contribute funds, proportionate to their budgets, toward a pool of resources that will support NIH Roadmap initiatives. This will ensure that a steady multi-year and flexible stream of funding is available. This approach, which establishes a corporate process for decision-making about trans-NIH priorities, should enable rapid responses to emerging opportunities that do not

do not clearly fit within the mission of a single or small group of ICs.

Additional information on NIH priority setting can be found in the NIH report "Setting Research Priorities at the National Institutes of Health," http://www.nih.gov/about/researchpriorities.htm.

Item

Office of research on women's health- The Committee remains strongly supportive of the work done by the Office of Research on Women's Health. In recent years, the office (working with various institutes) created the BIRCWH training program (Building Interdisciplinary Research Careers in Women's Health) and the SCOR (Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health) program. These have been major steps forward in women's health research. The Committee encourages the Director to provide adequate funding for ORWH so that it will be able to offer a second round of SCOR grants in FY04 and to expand the BIRCWH program. (p. 91)

Action taken or to be taken

Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs)

The Office of Research on Women's Health (ORWH), in collaboration with several NIH Institutes and the Food and Drug Administration (FDA), funded eleven SCOR programs. These interdisciplinary research programs have proved successful in mobilizing scientists of diverse disciplines to bring their scientific expertise to bear on examining how sex and gender factors contribute to health and disease. Such an effort would be instrumental in propagating this innovative interdisciplinary research approach to women's health research among seasoned extramural scientists.

Building Interdisciplinary Research Careers in Women's Health (BIRCWH)

The ORWH initiated an institutional mentored career development award for Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Career Development Programs. These Programs support research career development of junior faculty members, known as Interdisciplinary Women's Health Research (IWHR) Scholars, who have recently completed clinical training or postdoctoral fellowships, and who are commencing basic, translational, clinical and/or health services research relevant to women's health.

The ORWH initiated the BIRCWH program in FY1999 with cosponsorship from many NIH ICs and the Agency for Health Care Research and Quality (AHRQ). Twelve Centers were funded in FY 2000 and an additional 12 in FY 2002. This 5-year interdisciplinary career development program has proved very successful in ensuring a cadre of researchers transition smoothly from junior to senior status in areas of women's health research. To date, there are marked successes among the more than 100 scholars in the program who have advanced to a more senior faculty

level supported by the large number of research grants these scholars have already been awarded. In FY 2005, ORWH plans to issue a new RFA (BIRCWH III) for current and additional BIRCWH Centers to allow additional emphasis on sex and gender factors.

Item

Uterine fibroids– Twenty to thirty percent of women in the U.S. of reproductive age suffer from uterine fibroids, a benign tumor that affects their reproductive health. Research on treatment has been limited, and often women have unnecessary hysterectomies when less costly and invasive treatments may be possible. In conjunction with NICHD, NIEHS, and NCMHD, ORWH is encouraged to intensify and coordinate programs to support research on uterine fibroids. (p. 91)

Action taken or to be taken

ORWH continues to encourage and stimulate research on uterine fibroids and other benign gynecologic disorders. As part of this effort, ORWH collaborates with a number of the NIH ICs (NICHD, NIEHS, NCRR, NCI and NCMHD) to co-fund extramural research grants and to promote intramural research in this scientific area. All of these institutes and centers have extramural grants funded during FY 2003. In addition, ORWH currently co-funds a joint project with the Agency for Healthcare Research and Quality (AHRQ) on alternatives to hysterectomy.

ORWH is a co-sponsor with NICHD on a major new program initiative entitled, *Leiomyomata Uteri: Basic science and Translational Research*. This new program focuses on the biological processes that lead to the development of uterine fibroids, and their long-term sequelae.

The objective of this effort is to strengthen research in this critical area of women's health, to contribute to reducing the burden of this condition, and to improve the quality of life for women affected with this disorder. Eight new extramural grants are receiving funding under this initiative.

There are two NIH intramural research programs located at NIEHS and NICHD. The NIEHS-supported studies have shown the high prevalence of uterine fibroids in both African-American and Caucasian women. A new study focusing on the determinants of growth of these fibroids and the identification of markers for growth is being co-funded by NCMHD with NIEHS.

The Intramural Research Program at NICHD conducts translational research on the cause of uterine fibroids, specifically directed at identifying the molecular mechanisms responsible for
fibroid development. The current focus has been to identify genes abnormally expressed in fibroids compared to normal uterine muscle. The identification of the genetic profile of uterine fibroids may suggest new therapeutic strategies for treatment.

ORWH will continue to bring together the components of the NIH ICs to strengthen uterine fibroid research in both the extramural and intramural settings. NIH will continue

to encourage grant applications that will expand the knowledge base about uterine fibroids. Concerted efforts will also continue to raise greater awareness of the importance of uterine fibroid research at national scientific meetings, especially those attended by physicians and other clinical researchers.

Item

Office of Rare Disease Research-. . . . The Committee applauds ORD for its efforts to support the translation of basic research findings into improved treatments for orphan diseases. The Committee encourages the Office to increase its support for demonstration or pilot projects aimed at the development of interventions for orphan diseases, including cystic fibrosis. There is a pressing need for enhanced federal involvement in such programs, which are consistent with Congressional intent in passing the Rare Diseases Act of 2002. (p. 92)

Action taken or to be taken

On September 28, 2003, the Office of Rare Diseases (ORD) and NIH institutes and centers funded the Rare Diseases Clinical Research Network in response to the Rare Diseases Act of 2002, P.L. 107-280. The purpose of the network is to facilitate clinical research in rare diseases through a collaborative approach including pilot and demonstration projects. The NIH funded seven rare diseases clinical research centers and one data center. Each center provides components required of the total network including a clinical research trials program designed to test novel therapies, develop diagnostic tests, and evaluate outcome measures. In the Rare Lung Diseases consortium, ongoing clinical, basic, and translational studies at the participating centers have already provided insights into molecular mechanisms underlying lung function and defense in health and disease.

Regarding cystic fibrosis (CF) directly, in 2003, ORD cosponsored a scientific conference on CF with the National Heart, Lung, and Blood Institute (NHLBI.) Scientists evaluated the current state of knowledge of macro-molecular interactions that control ion transport processes in CF and developed recommendations for future research. The conference is expected to foster new basic and clinical research directions and scientific collaborations.

Also, the recently published, cosponsored program announcement by ORD with the NHLBI for pilot studies, demonstration projects, and exploratory research studies in rare heart, lung, and blood diseases could include CF. Awards will allow investigators with novel ideas to obtain research support without the need for large amounts of preliminary data that often serve as a barrier to entry into the NIH grants system. It is anticipated that these efforts will ultimately result in an increased pipeline of therapeutic approaches to treatment and prevention of a wide range of rare heart, lung, and blood diseases.

In addition, the Office of Rare Diseases is in the process of convening a trans-NIH rare diseases working group which should provide an additional means of collaboration in rare/orphan diseases research including pilot and demonstration projects and focusing on rare diseases including CF.

The NIDDK will sponsor a workshop in May 2004 on protein misfolding and misprocessing in disease. The objective of this workshop is to stimulate research that will translate basic cell biology, biochemistry and biophysics findings about protein structure

structure and assembly into potential therapies for monogenic disorders that are within the mission of NIDDK. This workshop has significance for cystic fibrosis, alpha-1 antitrypsin deficiency, and several other rare diseases in which both the NIDDK and the ORD have a shared research interest.

Item

Office of Rare Disease Research – The Committee notes the significant number of rare liver diseases including primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. The Committee encourages ORD to work closely with NIDDK to develop an appropriate response to address these significant diseases and to work toward a comprehensive research agenda. (p. 92)

Action taken or to be taken

The Office of Rare Diseases (ORD) works very closely with NIH institutes and centers and offices including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute (NHLBI). Within the area of rare liver diseases research, ORD is cofunding with the NIDDK the Biliary Atresia Research Consortium (BARC), which contains nine pediatric liver disease centers. The aims of this consortium are to develop and test hypotheses on the cause of biliary atresia and to help define the best means of diagnosis and management of this disease.

ORD cosponsored with the National Institute of Environmental Health Sciences (NIEHS) and the NIDDK and others a scientific conference on the emerging area of metabolic profiling and its application to the health sciences. Research scientists (molecular biologists, analytical chemists, toxicologists, clinicians, nutritional scientists, and computational biologists) defined the current state of the science in metabolic profiling and its application to the health sciences. Specific emphasis was placed on the application of metabolic profiling to toxicology and risk reduction. The conference provided a forum for identifying scientific initiatives needed to stimulate metabolic profiling research and to develop partnerships between academia, government, and industry with the hope of better treatments of metabolic and digestive diseases.

With regard to rare liver diseases, the NIDDK is committed to advancing knowledge of the autoimmune liver disease that encompasses three major diseases, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH). All three diseases are uncommon (each affecting 10-50 persons/100,000 population), but they are all capable of leading to end-stage liver disease, liver failure, and the need for liver transplantation. The NIDDK is funding large multi center trials of therapy both for PBC and PSC in the Clinical Trials Program of the Division of Digestive Diseases and Nutrition. In addition, both NIDDK and NIAID fund several basic research projects (R01s) in PBC, PSC and autoimmune hepatitis which focus on underlying causes of these diseases. In the past year, the NIDDK has made efforts to stimulate research in these important diseases. On June 16, 2003, the Digestive Disease Interagency Coordinating Committee, which the NIDDK chairs, held a half-day workshop on primary biliary cirrhosis, which focused on current status of understanding of this disease and the challenges for future research. In a similar manner, the NIDDK, in conjunction with the American Association for the Study of Liver Diseases (AASLD), has proposed a workshop on autoimmune hepatitis and needs for future research for November 2004. Importantly, autoimmune liver disease is one of the

Importantly, autoimmune liver disease is one of the 12 targeted areas in the "Action Plan for Liver Disease Research" that is being developed by Liver Subcommittee of the Digestive Disease Interagency Coordinating Committee, which

includes members of all NIH Institutes, Centers and Offices that fund liver disease-related research. A newly-formed NIDDK Liver Disease Branch is helping to spearhead this planning effort, in which the ORD will be asked to participate.

In February 2003, ORD with several NIH components cosponsored an RFA to establish a Rare Diseases Clinical Research Network. This solicitation resulted in the funding of seven Rare Diseases Clinical Research Centers, one of which was co-funded by the NIDDK for urea cycle disorders many of which have a significant liver disease component.

Item

Clinical research – The Committee commends the NIH leadership for their efforts to critically examine and to re-engineer the clinical research enterprise to more efficiently translate clinical research advances into new treatments and improved medical care. The Committee recommends that as part of the "roadmap" initiative, the Director develop recommendations for addressing these impediments, with special consideration given to: providing clinical research infrastructure support grants to eligible institutions; support and/or restructuring of the institutional review board system; and the harmonization and streamlining of NIH, FDA, NSF and DoD regulations governing clinical research. The Committee would like to hear NIH's response to these recommendations in the fiscal year 2005 hearings. (p. 93)

Action taken or to be taken

The NIH appreciates the Committee's recognition and support of the Roadmap initiative and its goal of transforming the national research enterprise to accelerate the development of treatments and cures for the nation's most vexing health care problems. Ensuring an environment in which publicly supported clinical research can be highly productive is a major emphasis of this endeavor, building on existing NIH mechanisms to promote and sustain the infrastructure essential for the flourishing of high quality science. Such programs as the General Clinical

Research Centers and an array of other infrastructure and training programs have long aimed to ensure the "critical mass" of highly skilled personnel and state-of-the-art resources necessary for a vigorous clinical research enterprise.

These programs to promote the vitality and productivity of clinical research will be greatly enhanced by two major components of the NIH Roadmap effort – the Clinical Research Networks Program and the Clinical Research Policy Coordination Initiative. Both efforts will enable more efficient translation of fundamental research findings into clinically beneficial products by promoting enhanced collaboration, shared infrastructure, and coordinated approaches to oversight and compliance.

The Clinical Research Networks initiative is designed to promote synergy among diverse clinical research activities through the development of linkages among research institutions, medical

centers, and existing research networks. Over time, this interconnectivity will progress until, ultimately, a national "network of networks" is created. The grants funded under this endeavor will create a revolutionary new clinical research infrastructure model, enabling greatly enhanced communication, computational capacities, access to resources, and research and analytical tools. Such a system will offer economies of scale by allowing complex research programs to benefit from a common infrastructure, rather than recreating infrastructure resources time and time again at multiple sites. Networking will enable broad access to data and allow investigators to learn from, utilize and build upon existing data, rather than conducting experiments already accomplished by others. Integration of data also permits the formulation and study of new research questions, tying together major fields of inquiry in the process.

The "central nervous system" of this endeavor will be the National Electronic Clinical Trials and Research (NECTAR) Network. NECTAR is an informatics infrastructure that will allow data systems used by various research institutions to communicate readily with one another. To accomplish this, NECTAR will create common vocabularies, research and business tools, and common platforms and architectures. Ultimately, NECTAR will allow:

- More efficient business practices and processes,
- Enhanced data sharing and analysis,
- Coordinated oversight and improved patient protections, and
- Rapid translation of research into clinical findings and practice.

The NIH agrees with the Committee that the efficiency and effectiveness of our system of clinical research is affected by the wide variability in regulations, policies and procedures that pertain to its conduct and oversight. Thus, the goal of NIH's Clinical Research Policy Coordination Initiative (CRPCI) is to create a focal point for working within the Federal system of clinical research oversight to promote the coordination of policies, requirements, and procedures concerning clinical research and, where appropriate, to help bring about streamlined approaches. The CRPCI will examine an array of issues and activities on behalf of all NIH ICs and help develop coordinated policies, practices and new tools for compliance that take account of the goals and points of view of NIH's varied organizational components and stakeholders. In particular, we share the Committee's focus on for Institutional Review Boards (IRBs). As the linchpin of our system of human subjects protections, IRBs will be a primary beneficiary of our efforts to streamline the oversight system. Some representative activities will include:

- Studying existing requirements for the conduct and oversight of clinical research to assess the extent to which unnecessary or duplicative rules can be addressed without diminishing protections;
- Developing tools and materials to help ensure and facilitate compliance with existing rules;
- Working with other Federal agencies (such as FDA, OHRP, DoD, and the VA) that fund, conduct, and oversee clinical research to promote the development of coordinated clinical research policies;
- Soliciting input on various policy goals from key communities, such as patients, scientists, institutional leadership, IRB members, and other constituencies with a stake in the conduct of clinical research; and

· Developing educational and training tools to assist investigators and IRBs in the interpretation and compliance with human subjects and related research requirements

Item

Practice-based clinical research networks – Clinical research is more important now than ever before to translate advances in basic science into better diagnosis, prevention, treatment, and cure of disease and to provide high-quality evidence of diagnosis and treatment effectiveness to fully integrate into daily practice decisions. Placing clinical studies at the community practice level will ensure adequate representation of patients from all age, sex, and cultural groups in clinical studies, and will also increase the number of practicing clinicians who are trained to undertake clinical research. A model for such networks has been established by the Agency for Healthcare Research and Quality (AHRQ). The Committee encourages the Director of the NIH to consider incorporating the AHRQ practice-based networks into NIH-supported clinical trials in order to include specialty practitioners who care for the most common health problems of the American people. (p. 93)

Action taken or to be taken

We appreciate the Committee's suggestion that the NIH Director consider incorporating AHRQ practice-based networks into NIH-supported research in order to include practitioners on the front lines who provide care for the nation's most prevalent health disorders. The NIH Director recognizes AHRQ's research networks, including its Primary Care Practice-Based Research Networks (PCPBN) and its Integrated Service Delivery Research Network (ISDRN), respectively, as research resources of considerable value to NIH-supported investigators. In fact, NIH and AHRQ leadership recently met to discuss possible collaborations.

Under auspices of the NIH Roadmap, NIH aims to make the sharing of data among a broad community of clinical researchers standard practice. We hope to accomplish this by fostering clinical research networks that are based on common and interoperable infrastructure elements, such as informatics, governance, common language and training activities. It is expected that this effort will broaden the kinds of research questions that can be addressed, as well as enhance the efficiency of conducting clinical research. These clinical research networks will also work with aligned groups to promote the rapid dissemination of study results into clinical practice. In addition to facilitating the conduct of translational research, these networks will be primed to incorporate the results of health services research into the next generation of research questions.

The networks will utilize the tools and systems developed under auspices of a NIH National Electronic Clinical Trials and Research Network (NECTAR). In addition, these networks will provide an infrastructure for launching the NIH National Clinical Research Associates, a corps of trained, community-based practitioners who care for large groups of well-characterized patients and work jointly on clinical trials.

Initially, NIH is taking steps to comprehensively assess best practices among the myriad of extant clinical research networks by conducting an inventory of national and

international, public and private-sector based networks. The inventory will encompass groups focused on research with under served populations, with disease-specific specialty groups, and with entities organized by locus of care, examining characteristics relating to network structure and goals. The inventory will help to catalogue the types and volume of studies, organizational and management structure, criteria for the evaluation of performance, informatics infrastructure, and training procedures of extant national networks. NIH is also soliciting feasibility studies in order to evaluate factors that either promote or serve as barriers to successful network interactivity and to the expansion, or
broadening, of network research scope. NIH will share the outcomes of its activities with AHRQ and seek to include AHRQ colleagues in the development of this new national interoperable clinical research network infrastructure.

Item

Physical sciences– The Committee recognizes that breakthroughs in the physical sciences underpin many of the remarkable advances in the life sciences that have been achieved during the last century. Biomedical research now involves not only molecular biologists but also chemists, bioengineers, bio-imaging experts, physicists, mathematicians, computer scientists, and other professionals. Increasingly, the boundaries between the life sciences and the physical sciences are being blurred, as capacities and talents bridging the disciplines are essential for modern experimentation and discovery. Accordingly, the Committee believes that a major effort must be undertaken to promote the advancement of research at the interface between the life sciences and the physical sciences. This interface occurs in many agencies including NIH, NSF, Office of Science, Department of Energy, DARPA, NASA, NAA, and others. The Committee suggests that NIH work with all such agencies to convene a conference to discuss what needs to be done to encourage progress in the physical sciences that will provide support and underpinning in the future for advances in the life sciences. (p. 94)

Action taken or to be taken

Because this request for NIH to convene an Interagency Conference on the Interface of Life Sciences and Physical Sciences is both trans-NIH and interdisciplinary in nature, it was added to the purview of the NIH Roadmap Interdisciplinary Research (IR) Teams of the Future Implementation Team. The proposed conference has been approved as a Roadmap initiative, with a commitment of central Roadmap funding for logistical support of convening the conference.

Dr. Lawrence Tabak, Director of the National Institute of Dental and Craniofacial Research (NIDCR), and a chair of the Roadmap IR Teams working group, is the NIH Co-Chair for this Interagency Conference, along with Dr. Roderic Pettigrew, Director, National Institute of Biomedical Imaging and Bioengineering (NIBIB). The co-chairs sent a request to the NIH Institute and Center (IC) Directors requesting their participation in the conference and its planning, and 16 ICs and OD offices have agreed to participate. Representatives from the trans-NIH Bioengineering Consortium (BECON) and the Biomedical Information Science and Technology Initiative Consortium (BISTIC) are included.

The sister agencies listed in the report language have also been contacted, and participants representing NSF, NASA, DOE, DARPA, NOAA, as well as FDA and NIST have been identified.

It should be noted that similar report language included in the House VA/HUD/Independent Agencies Appropriations Subcommittee report called for NSF to take a leadership role in this conference [House Rpt.108-235 (p. 143)]

> "NSF: RESEARCH AND RELATED ACTIVITIES
> While the National Institutes of Health has principal responsibility for research involving human health and disease, NSF has historically played a critical role in funding long range basic research and technology development which have been critical to NIH's more focused mission. NSF's work on the basic chemical processes which made possible the mapping of the human genome is perhaps the best known example of this extraordinarily important collaboration. The Committee believes that the future of scientific advancement in both the physical sciences and the life sciences will increasingly rely on such collaborations and urges the NSF to work aggressively with NIH to determine how this research can be strengthened. The Committee has recently asked the NIH to convene a conference of all the stakeholder agencies within the Federal government whose missions involve the conduct or support of research at the scientific interface between the life sciences and the physical sciences. ***NSF is encouraged to play a leading role in this conference, which will hopefully occur during 2003. The Director should be prepared to testify to the Committee at NSF's appropriations hearings on the 2005 budget on the results of this conference as they relate to NSF and on any changes in resource allocations or management systems within NSF which would strengthen this critical area of research."***

In addition, Conference Report Language acknowledges and commends NIH for its plans to convene the Conference [House Rpt.108-401 (p. 776) - Making Appropriations for Agriculture, Rural Development, Food and Drug Administration, and Related Agencies for the Fiscal Year Ending September 30, 2004, and for Other Purposes]:

> NIH OFFICE OF DIRECTOR
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> The conferees recognize that breakthroughs in the physical sciences underpin many of the remarkable advances in the life sciences that have been achieved during the last century. Increasingly, the boundaries between the life sciences and the physical sciences are being blurred, as capacities and talents bridging the disciplines are essential for modern experimentation and discovery. Accordingly, the conferees believe that a major effort must be undertaken to promote the advancement of research at the interface between the life sciences and the physical sciences. This interface occurs in many agencies including NIH, NSF, Office of Science, Department of Energy, DARPA, NASA, NOAA, and others. ***The conferees commend NIH for its plans to evaluate, as part of the NIH Roadmap process, what steps need to be taken to encourage progress in the physical sciences that will provide support and underpinning for future advances in the life sciences and to convene a conference to discuss this issue***

issue with other Federal agencies.

The NIH Co-chairs have held a conference call with Dr. Rita Colwell, Director NSF, to discuss overall plans and objectives for the Interagency Conference. A planning meeting with all the NIH and sister agency representatives will be held on January 28th to shape the Agenda/Program for the Conference. It is anticipated that the Interagency Conference itself can be convened in the early spring of 2004.

Item

Autism – The Committee encourages NIH to expand the research portfolios (basic and applied) at the Centers for Excellence in Autism as well as the Collaborative Programs for Excellence in Autism. The Committee strongly encourages NIH leadership, as well as individual institutes such as NICHD and NIMH, to coordinate a tissue bank program that will synchronize autism spectrum disorder brain banking and data management, and track research among all participants in the tissue collection program. The Committee further encourages NIH to work closely with the Interagency Autism Coordinating Committee in developing and implementing the matrix it is developing for autism spectrum disorder research. The Committee also encourages NIH to look at collaborative opportunities for joint projects and conferences with national autism organizations that will foster greater participation in research activities by investigators entering the field. (p. 94)

Action taken or to be taken

The institutes (NIMH, NICHD, NINDS, NIDCD, and NIEHS) funding the Studies to Advance Autism Research and Treatment (STAART) Centers have now established a network of 8 centers and are actively engaged in implementing major center-based and multi-site studies. The Collaborative Programs for Excellence in Autism have undergone peer review and funding for a new project period. Both networks are collaborating and expanding. A National Autism Brain Bank has been established by NIMH, NINDS, and NIDCD. Coordinated data management and tracking are supported by this new initiative. A program is planned to coordinate its activities with the tissue banks operated by NICHD. The NIH is participating directly in all the Interagency Autism Coordinating Committee activities, including those involved in developing and implementing a matrix for autism research. The NIH has played a major role in forming partnerships with national autism organizations to co-fund major research activities and present them in national venues.

Item

Autism – The Committee continues to be aware of concerns about reports of a possible association between the measles component of the measles-mumps-rubella (MMR) vaccine and a subset of autism termed autistic entercolitis. The Committee continues its interest in this issue and urges the Interagency Coordinating Committee to continue to give serious attention to these reports. The Committee also urges NIH to continue to pursue appropriate research that will permit scientific analysis and evaluation of the concerns that have been raised through all available mechanisms, as appropriate, including an attempt to replicate the molecular evidence of persistent measles virus infection in children with autistic entercolitis. The research should be pursued in a way that does not cause undue harm to the Nation's efforts to protect children against vaccine-preventable diseases. . . . The Committee encourages NIH to pursue the recommended research initiatives outlined in the Institute of Medicine's (IOM) Immunization Review Committee reports. These reports have identified the research

needed to better understand why a small number of children suffer severe adverse reactions to childhood vaccines. This research is important for developing better screening capabilities and enhancing the public confidence in the national immunization programs. (p. 94)

Action taken or to be taken

The NIH and the other members of the Interagency Autism Coordinating Committee (IACC) continue to be aware of, and continue to keep themselves informed about, the latest evidence of a proposed association between the measles component of the measles-mumps-rubella (MMR) vaccine and a subset of autism termed autistic entercolitis. NIH has substantially expanded its autism research portfolio over the past several years, and now funds many diverse research activities that are beginning to address issues regarding many different factors, both genetic and environmental, that may cause autism. The Centers for Disease Control, a member of the IACC, has funded a study that will systematically evaluate the molecular evidence of persistent measles virus infection in children with autism. The IACC, with leadership from the CDC, has undertaken a public autism awareness program and is evaluating the issues involved in a nationwide early screening program for autism.

Item

Genomics– The Committee recognizes the important role that genomics and genetics plays in the progression of disease and believes that every institute has a key role to play in moving genomics to the clinical setting through the use of next generation technologies. The Committee urges the Director to continue to ensure that the institutes and centers are pursuing every available opportunity to advance this critical research. (p. 95)

Action taken or to be taken

Year 2003 witnessed the announcement by the International Human Genome Sequencing Consortium, a collaborative effort led by the National Human Genome Research Institute (NHGRI) and the National Institutes of Health (NIH), of the successful completion of the Human Genome Project (HGP) more than two years ahead of schedule and under budget. Without the support and leadership of the NIH Director, the HGP would not have been completed. The Director is committed to ensuring that the NIH continues to play a vital role in the future of genomics, one of the critical areas of biomedical research.

With the completion of the HGP, we are now entering a new era of genomics research - understanding the structure and function of the human genome and its role in health and disease. In order to ensure coordination for these new activities, the NIH, led by NHGRI, developed a new "Vision for the Future of Genomics Research," that sets out a clear plan for future genomic research in three main areas: Genomics to Biology, Genomics to Health, and Genomics to Society. This vision, developed with the input of all the NIH Institutes and over 600 advisors, not only sets out grand challenges for the field of genomics, but also delineates the role of the NIH in reaching these goals. This vision will help the NIH Director coordinate the NIH efforts around genomics research as well as to inspire the current and next generation of biomedical researchers to improved diagnosis, prevention, and treatment of disease using the tools developed by the HGP. *A Vision for the Future of Genomic Research* can be found at www.genome.gov

Item

Physical inactivity and disease– The Committee encourages NIH to integrate current research concerned with the impact of physical inactivity on human health, as well as the molecular mechanisms underlying disease prevention and treatment by exercise/activity, into a coordinated NIH-wide strategic research plan that confronts physical inactivity as a major cause of chronic health disorders. Physical inactivity, as a major catalyst of disease, represents a leading cause of death in the U.S. and is a major contributor to obesity and Type 2 diabetes, other important predictors of morbidity and mortality. The Committee encourages NIH to stimulate research investigators to bring their research expertise to bear on physical inactivity and disease.
(p. 95/96)

Action taken or to be taken

The NIH supports many research efforts in the area of physical inactivity. Several studies include physical activity as an intervention to achieve and sustain weight loss in an effort to
prevent obesity, reduce the risk of type 2 diabetes, and control blood pressure and improve overall cardiovascular health. Additionally, the NIH promotes the importance of physical activity through a variety of education and public outreach programs.

Research efforts:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a number of studies that feature physical activity as an intervention aimed at lowering weight and reducing the incidence of co-morbid conditions. For example, people who are overweight or obese are more likely to develop type 2 diabetes. NIDDK-supported studies include:

- Look AHEAD (Action for Health in Diabetes), a clinical trial that is investigating whether increased exercise and reduced caloric intake – lifestyle interventions designed to promote and sustain weight loss – will improve overall health and cardiovascular outcomes in obese individuals with type 2 diabetes. Look AHEAD is sponsored by the NIDDK, with co-sponsorship by other components of NIH and CDC.

- A clinical trial aimed at reducing risk factors for type 2 diabetes in children and adolescents (STOPPT2D) using a school-based program designed to improve physical activity and diet has completed its pilot phase for assessing multiple parameters (including height, weight, lipids, and oral glucose tolerance testing). The pilot phase showed that large numbers of middle school children were willing to participate in the trial. The physical activity pilot phase is ongoing now.

- The Diabetes Prevention Program (DPP) clinical trial revealed that participants who lost 5 to7 percent or more of their body weight and who performed at least 150 minutes of physical activity per week reduced their risk of developing type 2 diabetes by 58 percent. The NIH is conducting a follow-up study, the DPP Outcomes Study (DPPOS), to assess the durability of the effect of the intervention on weight change and risk of developing diabetes and to determine whether the interventions reduce cardiovascular disease.

- In addition to multi-site clinical trials, NIDDK has an active RO1 research portfolio, with interventions designed both to increase physical activities as well as to decrease sedentary behaviors. Research topics include the role of moderate exercise in preventing long-term weight regain among obese adults; the prevention of obesity in children through schools to deliver moderate intensity, intermittent, physically active academic lessons; environmental interventions to reduce sedentary behaviors in obese children; and various studies in children to increase physical activity to prevent or reduce weight gain, risk of type 2 diabetes, and improve maintenance of weight loss.

The National Heart, Lung, and Blood Institute has a very active research portfolio in the area of physical activity as it relates to cardiovascular disease risk factors. The Institute currently supports numerous studies that either focus directly on physical activity or include physical activity as a major component. Many of these studies are testing intervention approaches to improve physical activity levels in specific populations, such as overweight or obese women,
low-income women, children, adolescents, college students, African Americans, and Hispanic populations. Institute-supported studies relating to physical activity and cardiovascular disease risk factors include the following:

- The PREMIER study tested an intervention for modifying multiple lifestyle behaviors at once to control blood pressure. Initial study findings were published in April, 2003, and showed that adults could reduce their weight, improve their fitness through increased physical activity, eat a healthy diet, and lower their blood pressure. Analysis of additional study data are underway.

- The Weight Loss Maintenance Trial (WLM), which was implemented in 2003, will compare two strategies to help participants who have lost weight maintain their weight loss for 2 ½ years. Both strategies include a strong focus on increasing physical activity.

- The Girls Health Enrichment Multi-site Studies (GEMS) is evaluating interventions to prevent obesity in African American girls aged 8-10 years. One study is testing an intervention that seeks to increase physical activity by providing after-school dance classes. The second study promotes eating a healthy diet in addition to increasing physical activity.

- The Trial of Activity in Adolescent Girls (TAAG), begun in 2003, is testing the effectiveness of a coordinated school and community-based intervention in preventing the decline in physical activity that typically occurs among girls during middle school.

- The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) began in 2002 and will determine whether exercise can reduce mortality and hospitalizations for patients with heart failure.

Future research activities in the physical activity area will focus on translating proven approaches to the public so that more people will regularly engage in physical activity and realize the health benefits of physical activity.

Scientific evidence is accumulating on physical activity as a means for the primary prevention of cancer. Nearly 170 observational epidemiological studies of physical activity and cancer risk at a number of specific cancer sites have been conducted. The evidence for decreased risk with increased physical activity is classified as convincing for breast and colon cancers, probable for prostate cancer, possible for lung and endometrial cancers and insufficient for cancers at all other sites. Several plausible hypothesized biological mechanisms exist for the association between physical activity and cancer and the National Cancer Institute's Division of Cancer Prevention (DCP) is supporting mechanistic research in preclinical models. The DCP is also supporting research which assesses physical activity as a contributing factor in population studies examining interactions between biomarkers and diet in cancer susceptibility. In addition, several grants focus on the role of physical activity in reducing fatigue, in improving quality of life in cancer patients who have had recent chemotherapy or who have been diagnosed with breast cancer.

The National Institute of Nursing Research (NINR) supports several health promotion and disease prevention studies in which either the therapeutic intervention is physical activity or the planned intervention results in increased physical activity; several of these studies target minority women and adolescents with diabetes. NINR also supports studies that aim to prevent complications of disease or delay the progression of disease, including studies to increase exercise to improve well-being and reduce depression in people with HIV/AIDS; increase physical activity among people with chronic obstructive pulmonary disease; increase physical

activity after cardiac rehabilitation among women who have had a myocardial infarction (heart attack); and to use exercise as part of a plan to reduce overweight status after childbirth. [NINR input]

Educational/outreach programs:

The National Diabetes Education Program (NDEP) has launched an educational campaign: "Small Steps, Big Rewards. Prevent Type 2 Diabetes." The program will educate people at risk of developing type 2 diabetes as well as physicians and health care providers about how changes in diet and exercise, resulting in modest weight loss, can dramatically reduce the risk of type 2 diabetes. This outreach effort grew out of the results of the NIH-sponsored Diabetes Prevention Program clinical trial. The NDEP is co-sponsored by the NIH and the CDC.

The Weight-control Information Network (WIN) is a national information service of the NIH that encourages people to maintain a healthy weight through increased physical activity and healthy
diets. WIN's efforts include "Sisters Together: Move More, Eat Better," a national initiative designed to encourage African American women to maintain a healthy weight by becoming more physically active and eating healthier foods.

Obesity, like most chronic health problems, is caused by complex interactions between genetic, environmental and behavioral factors. Basic research is needed to untangle these interactions and develop molecular intervention strategies. Simultaneously, a

more practical solution is to modify the environmental contributors responsible for the majority of the obesity epidemic. The National Institute of Environmental Health Sciences (NIEHS) is taking a three-pronged research approach to develop effective models to reverse the trend toward increased obesity by identifying successful strategies to: (1) change eating behavior, (2) promote a more active lifestyle, and (3) change the design of residential communities to make them more conducive to walking. A number of potential strategies are being considered. One of the more innovative ideas is to develop a children's television program, comparable to "Sesame Street" called "The Fitness Fighters." NIEHS is working with an Emmy Award-winning writer of "Sesame Street" and other children's television shows to develop the series.

The National Institute on Aging is working to translate research findings in action through its highly successful campaign to encourage older people to exercise. Since the campaign was launched in 1998, NIA has distributed over 600,000 copies of its exercise guide and over 90,000 copies of its companion video to the public. A Spanish-language version of the guide was published in January 2002; to date, nearly 28,000 copies have been distributed.

Exercise is also one of the topics highlighted on NIHSeniorHealth.gov. Developed by the NIA and the National Library of Medicine and launched in 2003, this web site is easy for older adults to read, understand, remember, and navigate. For example, the site features large print and short, easy-to-read segments of information repeated in a variety of formats -- such as open-captioned videos and short quizzes -- to increase the likelihood it will be remembered. Consistent page layout and prompts help users move from one place to another on the site without feeling lost or overwhelmed. The site also has a Atalking@ function, which allows users the option of reading the text or listening to it as it is read to them. The site focuses on health topics and specific diseases that are of particular interest to older people, with additional topics slated to be added. Each topic provides general background information, quizzes, frequently asked questions (FAQs), open-captioned video clips, transcripts for the videos, and photos and illustrations with captions. Since its launch, NIHSeniorHealth.gov has averaged over 17,000 page requests per day. [NIA input]

Coordination efforts:

In addition to these efforts, the NIH Director has established a trans-NIH Obesity Research Task Force. This group, which is co-chaired by the Director of the NIDDK and the Acting Director of the NHLBI, this task force will develop an NIH strategic plan for obesity research by identifying areas of greatest scientific opportunity, monitor and report on the plan's implementation, and
serve as the NIH point of contact on this issue with external agencies. One important aspect of the task force's work will be to promote research into ways to increase physical activity.

Also, the Office of Behavioral and Social Sciences Research (OBSSR) has organized a trans-NIH working group on physical activity. The mission of the Physical Activity Assessment Workgroup is to improve science with regard to the measurement of physical activity outcomes through cross-project collaboration and comparison.

Item

Research Infrastructure at Minority Health Professions Institutions- The Committee continues to be pleased with the NIH Director's implementation of various programs focused on developing research infrastructure at minority health professions institutions. The Committee recommends that the NIH Director work closely with the Director of the NCMHD to ensure coordination among these various mechanisms to partner with minority health professions schools to address their infrastructure needs. (p. 96)

Action taken or to be taken

Piloted in FY 2001, fully implemented in FY 2002 as an ongoing initiative, and expanded in FY 2003, NCMHD has plans to fund the Research Endowment program in FY 2004 and FY 2005. This program is an important priority of the Center and is considered to be an ongoing initiative. The Research Endowment Program generates funds to help build research and training capacity in institutions that make significant investments in the education and training of under represented minority and socio-economically disadvantaged individuals. The Research Endowment program seeks to 1) close the disparity gap in the burden of illness and death experienced by racial and ethnic minority Americans; 2) overcome educational and financial resource barriers to promote a diverse and strong scientific, technological and engineering workforce in the 21st century; and 3) increase the participation of under represented minorities in the biomedical, scientific, technological and engineering workforce. In addition to the previous year's awards, 4 Endowments were supported in FY 2003.

Fiscal Year 2003 was the second year of competition for NCMHD's Centers of Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Project EXPORT). Through this initiative, NCMHD funds collaborative research efforts, which enables institutions at all levels of capacity to maximize their health disparities research efforts. Through this program, the NCMHD will engage communities in the effort to eradicate health disparities; build research capacity at minority-serving institutions; promote participation in biomedical and behavioral research among health disparity populations; and increase participation in health disparities research. An additional 33 Project EXPORT awards were funded in FY 2003.

The Research Infrastructure in Minority Institutions program, originally administered by NCRR, is supported by NCMHD. These grants include an optional one-time allocation for relevant facilities renovations for which applicants may apply. NCMHD issued 5 awards in FY 2003. Each of the applicants requested and received this renovation funding.

NCMHD also collaborated with NCRR to support Bioethics Research at Tuskegee University through the completion of construction of the institution's National Center for Bioethics in Research and Health Care. This award allows the Tuskegee to provide research and teaching facilities for faculty, researchers and visiting scholars involved in bioethics, public health, and integrated bioscience programs.

The NIH Director worked closely with the Director of NCMHD to implement these research infrastructure programs. The NIH Director will continue to work closely with the NCMHD Director to coordinate these efforts to support the research infrastructure at minority health professions schools.

Item

Lupus - Lupus is an inflammatory autoimmune disease which affects more than 1.5 million Americans, 90% of whom are women. Lupus causes the immune system to attack the body's own cells and organs, including the kidneys, heart, lungs, brain, blood and skin. Lupus is two to three times more common among African Americans, Native Americans, Hispanics, and Asians, than among Caucasians. Lupus is a disease of rampant, uncontrolled inflammation caused by multiple genes. It already is known that genes which regulate how immune system cells recognize foreign invaders in the body, and genes that modify the immune response, are involved in lupus. Therefore, scientists know some of the specific proteins that trigger lupus. New strategies in molecular medicine can now be applied to improve the function of these proteins and prevent lupus flares. Because lupus is a multifaceted disease, the Committee encourages the Director to ensure that all relevant institutes are working closely and collaboratively to maximize the output of their investment in lupus research. (p. 96)

Action taken or to be taken

To foster new collaborations in lupus, the Office of the Secretary, DHHS, established a new Federal Working Group on Lupus. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) was chosen to lead this new Federal Working Group, which held its first meeting in the fall of 2003. The group's purpose is to exchange information and coordinate Federal efforts in lupus research and education. Representatives from all relevant NIH Institutes and Centers, DHHS agencies, other Federal departments, and voluntary organizations having an interest in lupus participated in the first official Working Group meeting in October of 2003. Exchanging information and coordinating Federal efforts are also guiding principles for the NIH Autoimmune Diseases Coordinating Committee (ADCC), led by the National Institute of Allergy and Infectious Diseases, which recently developed a comprehensive research plan for autoimmune diseases, including lupus.

In the fall of 2003, national leaders in lupus research came together to discuss the latest scientific opportunities at the "Lupus Today: Research Into Action" scientific conference. The meeting was co-sponsored by the DHHS Office on Women's Health, the NIH Office of Research on Women's Health, and the NIAMS, along with other NIH Institutes and Centers and several lupus voluntary organizations. Lupus researchers shared the latest scientific discoveries and what they mean for the current and future management of lupus. Panel discussions included: the future of lupus clinical trials, patient participation in clinical trials, and how lupus affects minority populations. Other topics covered at the conference included childhood lupus, cardiovascular lupus, neuropsychiatric lupus. Information on cutting edge clinical trials involving stem cell therapy and high dose cytoxan was also presented.

Item

Tuberous sclerosis - Tuberous sclerosis complex (TSC) is a genetic disorder that attacks many of the body's vital organs including brain, heart, kidneys, lungs, eyes and skin. TSC is characterized by tumor growth and lesions of the central nervous system

that can result in seizures, autism, mental retardation and kidney failure. An estimated 50,000 Americans are thought to suffer from TSC, but because it is not widely known by the general public, nor commonly recognized by medical professionals, the number of individuals with TSC could be far greater. Because of the effects of TSC on multiple organ systems, the Committee urges the NIH Director to formulate an NIH-wide research agenda and report on this effort during the FY 2005 hearings. (p. 96)

Action taken or to be taken

In July 2003, the NIH released a strategic research plan for TSC, spearheaded by NINDS, which defined the following long-term goals: determine the molecular and cellular basis of TSC; understand and treat the symptoms of TSC; understand the expression of TSC symptoms across the life span and identify factors that affect this expression, such as natural history studies; develop resources that accelerate TSC research, including a general clinical database of TSC patient information and new animal/cell line models; and create new research opportunities. While this strategic plan is intended for the entire TSC research community, the NINDS is already helping to implement many of the specific objectives. Several NINDS-supported studies are underway to investigate the relationship between mutations in the TSC genes and the development of neurological abnormalities. For example, NINDS-funded researchers are generating mice with TSC2 mutations expressed in specific organs to explore the pathogenesis of TSC in the brain, heart, and kidney, and using a rat model of TSC2 to explore the relationships between TSC gene mutations, central nervous system tumors, and seizures. Researchers are also employing genetic and biochemical strategies to identify new components of the molecular pathway through which the TSC genes control cell growth and proliferation, including a newly awarded grant that employs mouse models. Additional NINDS-supported projects are underway to examine tryptophan metabolism as a potential marker for epilepsy and autism in TSC patients, and to develop gene therapy strategies to control tumor growth in animal models of TSC. The

NINDS continues to reassess research needs and implementation strategies by sponsoring periodic meetings on TSC; this past year, NINDS sponsored a symposium on TSC at the annual Child Neurology Society meeting.

Item

Lymphangiomyomatosis (LAM)- The Committee remains very interested in efforts to find a cure for LAM, a progressive and often fatal lung disease with no effective treatment. The Committee understands that very recent scientific findings have presented new treatment approaches for clinical testing. The Committee urges the FDA, NCI, ORD and NHLBI to explore opportunities for funding clinical treatment trials through both intramural and extramural
means and to use all available mechanisms, as appropriate, including support state-of-the-science symposia and facilitating access to human tissues, to stimulate a broad range of clinical and basic LAM research. (p. 96)

Action taken or to be taken

The NHLBI supports a LAM patient registry that has enrolled over 240 patients. The registry also includes a LAM tissue repository for collection, processing, and distribution of fresh and stored LAM tissue for use in basic research. Investigators found a genetic abnormality in tuberous sclerosis complex (TSC) and LAM cells that results in a missing protein needed to control cell size and growth. This finding soon led the way to identifying a potential target for the treatment of LAM, and a pilot study is under way (not funded by the NHLBI) of rapamycin, a drug that mimics the function of the missing protein, in a small group of TSC and LAM patients. Investigators supported by the NHLBI also found that TSC gene mutations affect the motility of cells and permit LAM cells to metastasize. These discoveries provide insights into the cause and progression of LAM and suggest new treatment approaches. LAM can be difficult to diagnose, but NHLBI intramural scientists have developed clinical tests to identify LAM cells in blood, urine, and other body fluids; the availability of such tests may eliminate the need for invasive diagnostic lung biopsy. Investigators have also developed new tests to detect LAM cells in tissue of patients requiring surgery. In addition, clinical researches are using an exercise test to determine disease severity. Since 1995, the NHLBI has sponsored or co-sponsored a series of LAM meetings that have been instrumental in developing a research agenda for LAM. NHLBI staff also participate in a Rare Lung Disease Clinical Research Network that includes LAM and is sponsored by the NIH Office of Rare Diseases and the National Center for Research Resources.

Item

Asian-Pacific Islanders- According to the HHS report Healthy People 2010, the rapidly growing and diverse Asian American and Pacific Islander (AAPI) populations on the US mainland, Hawaii, and Pacific Regions, reflect a number of health disparities, including substance abuse. There is not adequate research data to address the increased incidence of substance use and abuse among AAPI youth and adults. The Committee urges NIH to increase its efforts to address the need for substance abuse research among Asian American and Pacific Islander populations.
(p. 96)

Action taken or to be taken

Since the early 1990s NIDA has been committed to filling significant gaps in knowledge about drug use by racial and ethnic minority groups, including Asian American and Pacific Islanders, and to addressing disparities in prevention and treatment. To help achieve these goals, in 1993,

NIDA established the Special Populations Office to increase the support of research on the social, behavioral, and health needs of minority populations. NIDA also established programs to encourage minority scholars to pursue careers in drug abuse research.

In 1999, NIDA established an Asian American and Pacific Islander Workgroup. This work group is comprised of a blend of researchers, scholars, practitioners, and community advocates. It provides guidance to NIDA on drug abuse related issues and needs among AAPI populations, and encourages AAPI students, researchers and

community-based organizations to participate in drug abuse research. Due to its concern about the lack of information available on drug use in AAPI communities, the Work Group has recommended that efforts be mounted to improve the epidemiological and knowledge base on drug abuse in AAPI populations. NIDA is exploring various strategies to address this, including discussing epidemiological data collecting efforts with SAMHSA in order to more systematically approach data collection activities.

NIDA is engaged in a number of activities in support of AAPI drug abuse research needs. NIDA has several studies that are looking at the drug abuse problem in Asian American populations.
NIDA has also provided support to the National Asian Pacific American Families Against Substance Abuse, Inc. (NAPAFASA), a national umbrella organization, that has been successful in drawing attention to alcohol and other drug problems in the Asian/Pacific Islander American population. A conference grant was awarded in 2003 in support of this meeting.

NIDA has also made concerted efforts to increase the number of under represented scholars involved in drug abuse research, primarily through the NIH's Minority Supplement Program.
This Program was established by the National Institutes of Health (NIH) to increase the numbers of under represented minority scientists participating in biomedical and behavioral research. NIDA considers Asians to be under represented in behavioral/clinical research. Funding is provided to current NIH research grants to support a minority student or investigator who wants to pursue a career in the biomedical or behavioral research sciences, through research experiences with NIH-funded investigators.

In 2002, NIDA supported two Health Disparities Supplements aimed at AAPI populations/issues. One of the NIDA supplements is aimed at obtaining an over-sample of Asian smokers in order to clarify the effectiveness of cessation treatment for Asian smokers, and to begin to gather baseline information for developing appropriately tailored cessation interventions for Asian smokers. Another supplement went to a researcher who is examining the complex relationship between domestic violence, substance abuse, and HIV related risks practices among a cohort of 300 plus self-identified Cambodian, Laotian, and Vietnamese women ages 18 and above living in the Washington, DC metropolitan area.

Also, as part of its efforts to raise awareness among cultural populations in the United States about the health risks of drug abuse and addiction, NIDA created a special 2003 calendar for Asian Americans and Pacific Islanders. With the creative recommendations of leading AAPI individuals and organizations nationwide, the rich histories of the many Asian, Native Hawaiian, and other Pacific Islander cultures are captured in each month's graphics and text selections, several of which include translations in various languages of the AAPI Communities. The AAPI calendar serves as a science-based resource on drug information, providing families and teachers with useful information to help them speak to children about the dangers of drug abuse in a way that incorporates the cultural richness and diversity of Asian Americans and Pacific Islanders.

NIDA has also disseminated findings about AAPI populations through a variety of venues, including three papers in Volume 117, Supplement 1, 2002 Public Health Reports, which emanated from the Health Disparities Conference NIH sponsored in 2001.

Since the early 1980s Asian American and Pacific Islanders have been the focus of NIAAA funded basic scientific investigation into the metabolism of alcohol. This sustained program of investigation has yielded valuable information about the role of genetic factors, including aldehyde metabolism, on risk and protective mechanisms in alcohol use and abuse. While these kinds of scientific investigations continue to be funded by NIAAA, it has also supported psycho social, behavioral, and epidemiological research. NIAAA is currently funding research on risk for alcohol use and abuse among Cambodian refugees and Asian American gang members. While information on the pattern of use and abuse of alcohol among the larger ethnic and racial minority groups is being developed rapidly, not as much is known about alcohol use among Asian Americans, Pacific Islanders and other Hawaiian Natives. As part of its efforts to develop the research infrastructure of minority serving institutions, to expand and improve health disparity research among minorities, NIAAA has recently collaborated with NCMHD to initiate a project at the University of Hawaii. One of the pilot research studies to be undertaken as part of this collaborative agreement will collect preliminary data on the prevalence of alcohol use in the multi-cultural Hawaiian population.

NIAAA has been involved in outreach and information dissemination activities in the Asian American, Pacific Islander and other Hawaiian Native populations. It has established a working relationship with National Asian Pacific American Families Against Substance Abuse, Inc. (NAPAFASA), a national umbrella organization, in order to enhance their efforts to draw attention to alcohol and other drug problems in the Asian/Pacific Islander American population. NIAAA funded a project to translate and publish health information on prevention of alcohol abuse information into Tagalog. NIAAA and SAMHSA co-sponsor National Alcohol Screening Day, a one day nation wide alcohol prevention and education event. NIAAA is presently working on plans to translate advertisement materials for National Alcohol Screening Day into at least one Asian language.

Item

Cooperation with the Department of Veterans Affairs– The Committee applauds the increasing research collaboration between NIH and the Department of Veterans Affairs and notes that the DVA system of 173 hospitals and 771 clinics represents a significant resource to facilitate and accelerate clinical research. In particular, the Committee encourages NIH to increase its cooperative efforts with the DVA to diagnose and manage the medical issues associated with hepatitis C and liver cancer. (p. 97)

Action taken or to be taken

The NIH has had a long relationship with the Department of Veterans Affairs and VA-supported research investigators. A major area of shared interest is liver disease, and specifically chronic hepatitis C, which is highly prevalent among VA Medical Center patients. Because alcohol

potentiates liver damage beyond what would be expected from the combination of hepatitis C and drinking, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) funds 60 research or research-training grants in this area. Many of the principal investigators hold dual appointments that include Veterans Affairs medical centers. NIAAA is cooperating with VA in several clinically relevant projects; for example, antifibrotic therapy in the treatment of liver disease. NIAAA and several other Institutes and Centers, as well as the NIH Office of Dietary Supplements, are considering jointly supporting a VA- proposed clinical trial assessing SAMe treatment of patients with alcoholic cirrhosis.

Collaboration between VA investigators and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is demonstrated in the two large NIDDK-supported studies on hepatitis C – Virahep-C and HALT-C – as well as the study of nonalcoholic steatohepatitis (NASH Clinical Research Network). Several investigators in these studies are based at VA facilities and therefore VA patients are full participants in these studies. The NIDDK's collaborations with the VA have been strengthened by the hiring of an internationally recognized investigator in hepatitis C, who spent well over 30 years working for the VA as a clinical investigator and as a program director in gastroenterology and hepatology. This individual leads an interagency working group on hepatitis C that has been active in initiatives in this area, including the planning and coordination of the 2002 NIH Consensus Development Conference on "Management of Hepatitis C" that was cosponsored by the NIDDK, seven other NIH Institutes, the Centers for Disease Control and Prevention, the Food and Drug Administration, the Center for Medicare and Medicaid Services, and the Veterans Affairs Administration. The staff of the newly formed NIDDK Liver Disease Research Branch, in collaboration with NCI, NIBIB and the VA, has recently organized a research workshop on "Hepatocellular Carcinoma: Screening, Diagnosis and Management" scheduled for April 1-3, 2004. Liver cancer is a major, almost universally fatal complication of cirrhosis due to hepatitis C, and is increasing in incidence in the U.S., largely as a result of hepatitis C and particularly among VA Medical Center patients. The NIDDK, with NCI, NIBIB, and the VA, expect to use this research conference to develop initiatives in research on liver cancer, and promote closer collaborations between VA and NIH-funded centers focusing on liver cancer.

The NIDDK has also recently entered a collaboration with the VA Cooperative Study Program to jointly fund and oversee a clinical trial testing optimum treatment for patients with acute renal failure. This study will be conducted at 18 sites operated by the Department of Veterans Affairs and nine other sites.

The Department of Veterans affairs cosponsored an international meeting on the Treatment of Hepatitis C (HCV) and HIV/HCV Coinfection in Drug Users on November 11-13, 2003. This was in collaboration with NIDA, NIDDK, NIAID, the Office of AIDS Research, NIH and HRSA,

DHHS. The meeting showcased the VA as the single largest provider of HCV and HIV care in the U.S. and how it is a model system for HCV care and treatment to be replicated outside the VA.

Item

Hepatitis C clinical trial research network- The Committee notes that the hepatitis C consensus development conference recommended the creation of a clinical trial research network focused on hepatitis C but also intended to be useful to advancing an understanding of hepatitis C co-infection with HIV and hepatitis B. Since this research affects several institutes, the Committee encourages the Director of NIH to monitor that such a network be broadly representative across NIH research portfolios. (p. 97)

Action taken or to be taken

In the last four years, the NIDDK has developed multiple clinical research networks in hepatitis C, each dealing with a specific but large area of high priority. Thus, the HALT-C trial is a contract-funded network of 10 clinical centers and a data coordinating center that has enrolled over 1000 patients with advanced hepatitis C in a prospective study of long-term therapy with peginterferon focusing upon prevention of complications of end-stage liver disease and liver cancer. This study has broad trans-NIH support, with cofunding from the NCI, NIAID, and NCMHD as well as industry support from Roche Laboratories and has a large number of ancillary studies directed at specific problems in hepatitis C, such as early detection of liver cancer, non-invasive assessment of fibrosis, biomarkers for disease progression, quality of life, neurological and psychiatric symptoms of hepatitis C and side effects of therapy. The Virahep-C trial is a cooperative agreement network of 8 clinical centers and a data coordinating center that has enrolled 400 patients (half African-American and half Caucasian) into a study of peginterferon and ribavirin focusing on the cause of resistance to antiviral therapy. This study has four specific ancillary studies focusing on the important areas of host genetic markers for disease severity and response to interferon, interferon-signaling during antiviral therapy, immunological correlates of disease progression and antiviral response, and virological factors that determine response rate to treatment. The A2ALL study is a cooperative agreement network of 9 clinical centers with expertise in liver transplantation and a data coordinating center that will establish both retrospective and prospective cohort studies on living and deceased donor liver transplantation. This study is currently designing a trial of peginterferon and ribavirin therapy for hepatitis C in patients with advanced liver disease awaiting transplantation. This study has cofunding from HRSA and will solicit funding for ancillary studies from other Institutes and industry to more fully support this study. The Peds-C trial is a newly funded cooperative agreement with 11 clinical centers and a data coordinating center that will enroll approximately 120 children with chronic hepatitis C into a study comparing peginterferon alone to peginterferon and ribavirin. This study will provide long-term follow up on the children and special studies of growth and development to document the long-term safety and efficacy of therapy in this important population. This study has cofunding from the FDA and from Roche Laboratories. Further support using ancillary studies will be sought with other Institutes.

Other issues raised by the Consensus Development Conference panel in hepatitis C are being addressed through collaborations with other Institutes. Thus, the issue of hepatitis C in active drug users is a special focus of research by NIDA who recently held a symposium on this topic, co-funded by the NIDDK and NIAID. The issue of hepatitis C and alcohol has been the special focus of NIAAA in several RFAs and pilot studies of the interactions of alcohol and hepatitis C in cell culture systems, animal models and in humans. The problem of hepatitis C in kidney disease patients was the focus of an NIDDK sponsored workshop entitled "Hepatitis C and Renal

Disease" held on October 21-22, 2002. Several clinical trials of therapy of hepatitis C in renal disease patients are being funded by industry and by the NIH (an intramural study of peginterferon and gradual increasing doses of ribavirin). Hepatitis C infection in HIV infected individuals is the focus of research by several institutes including NIAID, NIDDK, and NIDA. The institutes support research to advance the understanding of the pathogenesis of HCV in HIV-infected individuals, in addition to treatment trials to determine the safety and efficacy of HCV treatments. The Adult AIDS Clinical Trial Group (AACTG) launched several clinical studies to investigate treatment of HIV-positive patients with hepatitis C, and recently assembled an advisory committee to lead the AACTG's research efforts

Thus, instead of establishing a single large network in hepatitis C, the NIDDK and other Institutes with interest in this disease have established multiple clinical trials and networks that deal with the specific issues of therapy of this disease, that go beyond the expertise possible in a single network and that rely upon peer review to guarantee the most rigorous quality of the clinical research.

Item

Parkinson's disease – The Committee supports the Director of NIH in his commitment to develop and implement a thorough plan for Parkinson's research. The Committee encourages NIH to devote resources to implement the plan developed using all available mechanisms and to consider including Parkinson's disease as a key part of the Director's clinical and translational research "roadmap" supported with the Director's discretionary fund. (p. 97)

Action taken or to be taken

The NIH continues to aggressively implement the Parkinson's Disease Research Agenda and to address all identified research opportunities and roadblocks in its search for a better understanding of the disease, improved treatments, and interventions for preventing or delaying its onset. Scientific participants at a Parkinson's disease (PD) Coordination Summit in 2002 provided the recommendations that form the basis for the most current set of specific goals in this area: the PD Matrix. These short-to-long term, and low-to-high risk action items were designed to target needs and to overcome roadblocks in the research community. The NIH is actively addressing these action items, both through new and expanded individual Institute and Center efforts, and through improved coordination and collaboration with other federal programs and the voluntary Parkinson's community.

The NIH "Roadmap" initiatives, being developed with input from a broad range of NIH staff and extramural scientific experts, are not disease- or discipline-specific, but rather take a cross–cutting approach to identifying scientific challenges and roadblocks to progress. Driven by the enormous convergence in fundamental research approaches and technologies across diseases, organs and biological systems, the Roadmap focuses on facilitating and accelerating multi-disciplinary aspects of basic, translational, and clinical research. Roadmap initiatives will exploit new opportunities and technologies that will accelerate progress in disease areas across the 27 Institutes and Centers of the NIH. The exact nature of this acceleration, and how long it will take to be realized, will differ depending on the nature of the initiative and current state of knowledge about a disorder. Some diseases, which are in need of further basic research, will be enhanced significantly by Roadmap initiatives exploring "New Pathways to Discovery." Other diseases

diseases will benefit more from Roadmap efforts aimed at optimal translation of existing discoveries into clinical reality, such as those designed for "Re-engineering of the Clinical Research Enterprise." Parkinson's disease will likely benefit from Roadmap initiatives across this spectrum - from the development of molecular libraries to enhance the discovery of small molecules in order to accelerate the availability of promising new drugs, to the creation of better integrated networks for conducting clinical trials.

Item

Rett syndrome– The Committee encourages NIH to target its research efforts to ascertain how the MECP2 and its protein affect other genes and tissues during the development of the nervous system and to develop animal models, as well as genotype and phenotype investigations of Rett syndrome. The Committee notes there is a need for expanded research on the daily problems that affect children with Rett syndrome, including autonomic disorders, such as respiratory, gastrointestinal, circulatory and cardiac disorders, seizures, and scoliosis. Additionally, the Committee recognizes that research in applied areas such as interventions and technological aids for improved literacy and communication will improve the quality of life for Rett syndrome patients and those with other communicative disorders. Since Rett syndrome is a multi-faceted disorder, the Committee encourages NIH to promote continuity across Institutes in their Rett syndrome research. (p. 97)

Action taken or to be taken

NIH continues to fund a range of research with implications for Rett syndrome. While mutations in the MeCP2 gene were recently discovered to cause Rett syndrome, the molecular events leading from MeCP2 mutations to neurologic deficits are unknown. As MeCP2 is a DNA-binding protein that regulates gene expression, NIH is funding several projects to identify genes that may be misexpressed in Rett syndrome. Studies are also underway to define the neurodevelopmental defects in Rett syndrome by various microscopy techniques, develop new mouse models for pathogenesis and therapeutic studies, and test whether methyl donor drugs (e.g., folate) can reduce neurological dysfunction in Rett patients. To encourage additional research, NINDS and NICHD recently released a Program Announcement to solicit grants on developmental, molecular, and pathophysiological research; therapy development; and clinical studies of Rett syndrome.

In follow up to the 4th Annual Rett Syndrome Symposium meeting held in Baltimore, the NIH has been involved in organizational discussions for an International Rett Syndrome Committee on Clinical Trials meeting this Spring to discuss global clinical trials. In addition, NIH interactions with the International Rett Syndrome community continue to expand, particularly with respect to fostering research on this important cause of mental retardation and autism in females.

During FY 2003, NICHD, the NIH Office of the Director, and the NCRR co-funded two new centers through the Rare Disease Cooperative Research Center initiative, affiliated closely with
existing Mental Retardation and Developmental Disabilities Research Centers. One of these is located at the Baylor University College of Medicine in Houston, TX and involves

involves an active research program on Rett syndrome.

Item

Research training – The Committee recognizes the continuing need for young investigators and clinical scientists, and encourages NIH to increase its support for research training and loan repayment programs. The Committee is aware that the National Academy of Sciences is currently conducting its Congressionally-authorized study of research personnel needs with regard to the National Research Training Awards. This Committee has expressed interest in this study in the past, and is looking forward to receiving NAS's recommendations with regard to health research training priorities. (p. 97/98)

Action taken or to be taken

We appreciate the Committee's continuing interest in the NIH research training programs and the quadrennial needs assessment conducted by the National Academy of Sciences (NAS). The Committee should know that the NAS study is underway and a report is expected before the end of calendar 2004

Item

Prevention research and training - The Committee recognizes that NIH has a broad portfolio of prevention research programs and encourages the Director to continue collaborating with CDC in order to maximize health returns for the American public. (p. 98)

Action taken or to be taken

Over the years, the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) have established numerous collaborative activities. The agencies are engaged in a broad range of joint projects and initiatives, including clinical and epidemiologic research, demonstration projects, health information dissemination, and sponsorship of workshops and conferences. Most recently, the two agencies have been working towards implementing the goals of the President's HealthierUS Initiative by establishing joint projects on diabetes, obesity, heart disease, and cancer, as well as on the associated risk factors such as physical activity and good nutrition. In FY 2003, to enhance cooperation and collaboration, the directors of NIH and CDC each designated a high-level official at their respective agency to serve as principal liaison. These individuals communicate on a regular basis to discuss matters of joint concern and to identify potential areas of collaboration. Through the individual institutes and centers in particular, the NIH continues to seek ways to establish additional cooperative projects with CDC to build an effective and efficient partnership addressing a spectrum of public health issues. We are gratified that these efforts are recognized by the House Appropriations Committee.

Item

Pseudo-xanthoma elasticum - Pseudo-xanthoma elasticum is a rare inherited skin disease that is often not visible in early life, but in more severe cases may manifest in childhood. The disorder involves the elastic tissue in the skin, but also can result in macular degeneration and hardening of the arteries. The Committee encourages NIH, through NIAMS, NEI and NHLBI, to support

research regarding treatments and cures for pseudo-xanthoma elasticum. (p. 98)

Action Taken or To Be taken

Pseudoxanthoma elasticum (PXE) is an inherited disorder involving the elastic tissue in the skin, eyes and cardiovascular system. Several years ago researchers identified the defective gene underlying PXE. Based on this finding researchers now believe that PXE is a metabolic disorder that results from chemical changes in body tissues. This discovery offers hope for the development of treatments based on metabolic changes such as diet or drug therapy. NIAMS investigators are currently studying genes on chromosome 16p13.1 to further understand the factors that regulate the expression patterns of this defective elastic gene (the gene responsible for building tissue). Uncovering these gene expression patterns will allow the early identification of affected individuals so that treatment can begin before the symptoms of the disease appear, and hopefully early enough to prevent such symptoms from ever developing.

Item

Hyperbaric oxygen- Based on anecdotal evidence collected by clinicians in the field of hyperbaric medicine, hyperbaric oxygen therapy (HBOT) is currently in widespread use in medical practice. NIH is encouraged to support meritorious research in this area, especially in basic science, in order to gather evidence regarding the efficacy of HBOT. When appropriate, clinical studies to test the safety and efficacy of this treatment for a variety of conditions, such as organ transplantation, limb reattachment, and before and after surgical procedures involving tourniqueting of extremities, as well as for treatment of hermorrhagic shock, brain injury, multiple trauma injury and multiple trauma crash injury, should be conducted. These studies should include adult and pediatric populations when possible. NIH is also encouraged to work with professional organizations interested in HBOT as this research moves forward to understand which new interventions are more effective than existing practices, which groups of patients are most likely to benefit, the degree of improvement compared to the cost, and the relative risks for the patient of alternative interventions. The Director is encouraged to make this type of research a higher priority across each of the Institutes and centers and report to the Committee at the end of fiscal year 2003 a summary of grants awarded. (p. 98)

Action taken or to be Taken

A number of NIH Institutes and Centers have supported, and continue to support, research on hyperbaric oxygen therapy, including studies of the use of HBOT in treating brain damage resulting from trauma, stroke, and exposure to radiation during brain tumor treatment; head and neck cancer; wound repair; and in improving in vitro fertilization treatment. Although many HBOT studies are conducted in animal models, several of the currently-funded projects do involve the evaluation of this therapy in human subjects. The NIH continues to be interested in supporting meritorious pre-clinical and clinical studies of HBOT, as appropriate for each specific indication, and welcomes applications in any promising area of research. The NIH has met with staff of professional organizations, as well as with prospective applicants and others interested in HBOT, and will continue to do so to encourage well-designed research in this area.

Item

Graduate training in clinical investigation awards – The Committee is concerned that

that NIH has not implemented the graduate training in clinical investigation awards program. This program was authorized in the Clinical Research Enhancement Act to provide tuition and stipend support for students seeking advanced degrees in clinical research. The awards were intended to complement the NIH clinical research curriculum awards, a major NIH initiative aimed at establishing training programs to reverse the shortage of well-trained clinical investigators. While the Committee is pleased that numerous curriculum awards have been provided across the country, it is concerned that these awards do not include student stipend/tuition awards. The Committee encourages NIH to implement training in clinical investigation awards in 2004 or to report to the Committee by March 1, 2004 why it has chosen not to do so. (p. 93)

Action taken or to be taken

We appreciate the Committee's interest in clinical training and would like to point out that the program referred to as the Graduate Training in Clinical Investigation Awards in the Clinical research Enhancement Act was implemented in November, 2001 as the Mentored Clinical Research Scholar Program. Please see the announcement at http://grants1.nih.gov/grants/guide/rfa-files/RFA-RR-02-001.html). This program provides institutional grants to medical centers with strong clinical research programs and supports the salary and tuition requirements for clinicians training to become independent, patient-oriented researchers. In many cases, the participants in these programs benefit from additional funding
offered by the Clinical Research Curriculum Development Award (K30). In FY 2003, the National Center for Research Resources made a total of 17 K12 awards at a total cost of nearly $13 million.

FY 2004 Senate Appropriations Committee Report Language (H. Rpt. 108-81)

Item

[Reprogramming] **–** The Committee directs the Director of NIH to make a written request to the chairman of the Committee prior to any reprogramming of $1,000,000 or more, between programs, projects, activities, institutes, divisions, and centers. The Committee desires to have the requests for reprogramming actions which involve less than the above-mentioned amounts if such actions would have the effect of changing funding requirements in future years, if programs or projects specifically cited in the Committee's reports are affected, or if the action can be considered to be the initiation of a new program. (p. 166)

Action taken or to be taken

The NIH agrees that dollar changes of less than $1,000,000 by mechanism or program, project, or activity do not represent a significant divergence from the intent of the Congress and provides much-needed flexibility to program directors to capitalize on emerging scientific opportunities. The NIH will continue to forward notifications to the Committees of reprogramming actions in excess of $1,000,000, or for those reprogramming actions affecting programs or projects specifically cited in Committee reports or that would initiate new programs.

Item

Autism- The Committee encourages NIH to expand the research portfolios at the existing Centers for Excellence in Autism as well as the existing collaborative programs for excellence in autism. . . . .The Committee further encourages NIH to work closely with its Interagency Autism Coordinating Committee in developing, implementing, and funding its matrix for autism spectrum disorder research. The Committee also encourages NIH to look at collaborative opportunities for joint projects and conferences with national autism organizations that will foster greater participation in research activities by investigators entering the field.
The Committee further urges the NIH to provide more attention and resources to autism research. In particular, to support and expand the Startt centers and ensure that all large autism projects adhere to principles of sharing of data and genetic material. Data sharing is one of the most effective and economical ways to increase the rate of discovery. The opportunity now exists to create large, integrated data sets encompassing data from CPEA, STARTT, CADRE and NIEHS centers. (p.166)

Action taken or to be taken
The institutes (NIMH, NICHD, NINDS, NIDCD, and NIEHS) funding the Studies to Advance Autism Research and Treatment (STAART) Centers have now established a network of 8 centers and are actively engaged in implementing major center-based and multi-site studies. The Collaborative Programs for Excellence in Autism have undergone peer review and funding for a new project period. Both networks are collaborating and expanding. NIH played a leadership role in developing the initial version of the Interagency Autism Coordinating Committee (IACC) matrix for autism spectrum disorder research, and it is playing a major role in developing an implementation plan and in undertaking the high priority items in the matrix. The NIH provided leadership for holding the Autism Summit meeting in November 2003 which prominently featured the role of voluntary organizations and their partnerships with NIH and CDC. The NIH has played a major role in forming partnerships with national autism organizations to co-fund major research activities. A National Autism Brain Bank has been established by NIMH, NINDS, and NIDCD. Coordinated data management and tracking are supported by this new initiative. A program is planned to coordinate its activities with the tissue banks operated by NICHD. The NIH has implemented sharing of data and materials in the STAART network, the CPEA network, and broadly across the autism field, in large part through collaborations with voluntary organizations.

Item
Autoimmune Diseases — The Committee strongly urges the Director to oversee the implementation of the December 2002 NIH Autoimmune Diseases Research Plan, which was requested in the Children's Health Act of 2000. (p. 167)

Action to be taken
The National Institutes of Health (NIH) remains deeply committed to research to improve the diagnosis, prevention, and treatment of autoimmune diseases. In December 2002, NIH transmitted the NIH Autoimmune Diseases Research Plan to Congress, in fulfillment of the requirements for a plan and biennial report under the Children's Health Act of 2000 (P.L. 106-310).

The NIH Autoimmune Diseases Research Plan was prepared by the NIH Autoimmune Diseases Coordinating Committee (ADCC) and reviewed by an expert panel that included scientists, clinicians, and representatives from constituency groups. The ADCC, which was established in 1998, under the direction of the National Institutes of Allergy and Infectious Diseases, facilitates collaboration among those NIH Institutes, Offices, and Centers, other Federal agencies, and private organizations with an interest in autoimmune diseases.

The ADCC Research Plan is a comprehensive, long-term agenda for autoimmune diseases research which describes four areas central to progress for all autoimmune diseases and offers recommendations for addressing them. These areas are: burden of disease; etiology; treatment, prevention, and diagnosis; and training, education, and information dissemination. The Plan highlights many unprecedented opportunities to increase the understanding of autoimmune diseases, with a conceptual focus on the underlying mechanisms shared by many autoimmune diseases. Understanding the commonalities of this family of heterogeneous diseases may facilitate the translation of new knowledge into more effective treatment and prevention strategies.

Since submitting its report to Congress in December 2002, the NIH ADCC has initiated a comprehensive inventory of initiatives and activities in autoimmune diseases research and associated components of the plan that are addressed by these efforts. This inventory will identify research supported by the many NIH Institutes and Centers who support research on autoimmune diseases, including the National Institute of Allergy and Infectious Diseases, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Eye Institute, the National Institute of Neurological Disorders and Stroke, and the National Heart, Lung, and Blood Institute, to name just a few. In addition, it is anticipated that this process will be extended to ADCC members outside the NIH, including the Centers for Disease Control and Prevention, the Food and Drug Administration, the Health Resources and Services Administration, and the Department of Veterans Affairs as well as private organizations.

The inventory will identify areas of the plan that are being addressed and those areas that may need additional effort. When this inventory is completed, the NIH ADCC will be able to provide a more detailed report on the status of implementation of the ADCC Research Plan.

Item

Chronic Fatigue Syndrome The Committee is disappointed that since NIH released its long awaited CFS program announcement in December 2001, it has yet to reverse 8 years of declining CFS research funding. The Committee urges the NIH to issue an RFA that would emphasize multidisciplinary studies to understand the cause and progression of CFS in adults and children as well as identify diagnostic markers and effective treatments. (p.167)

Action taken or to be taken

Program announcement PA-02-34, Pathophysiology and Treatment of Chronic Fatigue Syndrome (CFS) encourages basic, clinical and translational research ,with an emphasis on multi- and interdisciplinary team approaches, on the causes, consequences and treatment of CFS in diverse groups across the lifespan. The first applications acknowledging this program announcement were received for scientific council review in October 2002 and several have been funded. One, in particular, a 5-year prospective study of CFS in adolescents, a group on whom there is little published research, was among the applications meeting the criteria as detailed in the program announcement as well as scientific review criteria. This study, jointly funded by the Office of

Research on Women's Health (ORWH) and the National Institute of Child and Human Development (NICHD), should provide us with better information to address the Committee's concerns.

The ORWH, through the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome (CFSWG), plans to begin work on an RFA based on the findings from a scientific workshop, *Chronic Fatigue Syndrome: Neuroimmune Mechanisms* held in June 2003. This collaborative RFA will provide an opportunity to increase CFS research funding. Another result of that
workshop is the beginning of a collaborative effort with the intramural scientific community to address CFS, and similar multisystemic conditions of unknown origin, using the tools of scientific integrated medicine.

Rather than decreasing, NIH funding for CFS is increasing. The two low years of funding since 1994 were $5.9 million in 1999 and $5.8 million in 2000. In FY2002, actual NIH spending on CFS research was $7.2 million and is estimated to be $7.5 and $7.7 million for FY2003 and FY2004, respectively. It is also noted that the number of grants assigned for scientific council review increased from 5 in January 2002 to 15 in January 2004, thus demonstrating the potential for even more funding for CFS research.

Item

Cooperation with the Department of Veterans Affairs – The Committee applauds the increasing research collaboration between NIH and the Department of Veterans Affairs and notes that the DVA system of 173 hospitals and 771 clinics represents a significant resource to facilitate and accelerate clinical research. In particular, the Committee encourages NIH to increase its cooperative efforts with the DVA to diagnose and manage the medical issues associated with hepatitis C and liver cancer. (p. 168)

Action taken or to be taken

Please refer to page OD-65 of the document for the OD response to this item regarding Cooperation with the Department of Veterans Affairs.

Item

Distribution of Resources - The Committee is concerned, in light of the doubling of the agency's budget over the past 5 years and the rapid encroachment of new medical research challenges such as SARS and threats of bioweapons, that the agency has not

moved more rapidly towards encouraging funding of large scale collaborative efforts to address these and other medical challenges. While the pace of new challenges has increased, review time for proposals submitted to the Institutes at NIH continues to average about 18 months. The Committee strongly encourages the Director to develop means of encouraging large scale multi-institution projects to address significant areas of medical research and to devise means of reducing the time frames between a submission of a proposal and the grant award. (p. 168)

Action taken or to be taken

During the period from 1997 to 2003 the NIH substantially expanded the use of large scale grants, and multi-institution projects. To provide some sense of this expansion; in FY 1997, the NIH supported 1,414 research centers and cooperative clinical research awards at a total cost of $1.32 Billion. By FY 2003, the number had expanded to 1,840 awards at a total cost of $2.97 Billion. The Director's Roadmap Initiatives featured at http://nihroadmap.nih.gov/index.asp will further encourage the development interdisciplinary and network approaches.

With regard to emerging infectious diseases including SARS and organisms that might be used as bioweapons, the National Institute on Allergy and Infectious Diseases (NIAID) has launched a number of new programs to address these important public health issues. For example, in FY 2003, NIAID awarded grants for the Regional Centers of Excellence for Biodefense and Emerging Infectious Disease Research (RCE), the Regional Biocontainment Laboratories (RBL), and the National Biocontainment Laboratories (NBL). The RCEs will support investigator-directed research; train researchers and other personnel for biodefense research activities; create and maintain supporting resources, including scientific equipment; emphasize research focused on the development and testing of vaccine, therapeutic, and diagnostic concepts; make core facilities available to approved investigators from academia, government, biotech companies, and the pharmaceutical industry; and provide facilities and scientific support to first responders in the event of a national biodefense emergency. Each center comprises a lead institution and affiliated institutions located primarily in the same geographic region. The objective of the NBL program is to provide funding to design, construct, and commission comprehensive, state-of-the-art biosafety level (BSL)-4, BSL-3, and BSL-2 laboratories, as well as associated research and administrative support space; the RBL construction program will provide funding for similar facilities containing BSL-3 and BSL-2 labs. The RCEs, NBLs, and RBLs, will be part of the NIAID RCE Biodefense Network. The labs will serve as national and regional resources, will offer preferential support for the research activities of the RCEs and other NIAID-funded biodefense research, and will be available and prepared to assist national, State, and local public health efforts in the event of a biodefense emergency. Extensive information on the NIH response to emerging infectious diseases can be found at http://www.niaid.nih.gov/default.htm.

Nearly all NIH grants are funded within 10 months of receipt. In some cases, this process has been accelerated by *en bloc* council review and other approaches that have permitted a reduction in processing time to 6 months or fewer. It is our hope that electronic applications will offer additional economies in this regard. Reducing the time

from receipt to award will remain a high priority for the Director and the NIH.

Item

Education and Health—The Committee is interested in the trans-NIH request for applications, initiated by the Office of Behavioral and Social Sciences Research [OBSSR], to better understand how education contributes to health. Better scientific understanding of the causal pathways between education and health could lead to new or improved prevention and therapeutic intervention strategies for important health problems. In some but not all studies of clinical treatments, those with lower levels of educational attainment demonstrated poorer outcomes. The Committee looks forward to hearing about new research directions in this important arena. (p. 168)

Action taken or to be taken

The Office of Behavioral and Social Sciences Research in collaboration with the National Institute on Aging, National Cancer Institute, and National Institute of Child Health and Human Development released a Request for Application (RFA) entitled ***Pathways Linking Education to Health*** in fiscal year 2003.

The goal of this RFA was to increase the level and diversity of research directed at elucidating the causal pathways and mechanisms that may underlie the association between education and health. Better scientific understanding of the causal pathways between education and health could lead to additional and improved prevention and therapeutic intervention strategies for important health problems. In order to better understand these pathways, validation of specific measures of abilities crucial to educational attainment, such as level of cognitive or language skills, is needed. Further exploration of intervening neuro- or psycho biological mechanisms, such as impact on frontal lobe structure or function or psychological characteristics, is needed and how these relate to a significant health outcome or important health related behavior.

Applications in response to the RFA were reviewed by a Special Emphasis Panel convened by the Center for Scientific Review, NIH, on July 15, 2003. Thirteen research grants have been selected for funding. These studies feature a variety of strategies ranging from the demographic tradition of a nationally representative longitudinal study to epidemiological approaches with special populations, to a ‘twin’ study and social experiments.

The funded grants are three-year projects from research universities across the nation. The age groups targeted in these studies range from early childhood to older adults. The specific diseases that are the focus of these projects range from cancer to diabetes. Some of the projects are highly relevant to multiple health problems such as the role of education in self-management and patient adherence to complex medical treatments. A range of research approaches is used in these studies. The principal investigators are from a variety of disciplines such as sociology, internal medicine, and economics. Overall this collection of research grants meets the goals of the RFA and will advance our understanding of the pathways that link education to many health problems.

Item

Epilepsy - The Committee recognizes that while the NINDS is the primary Institute for addressing epilepsy, several other Institutes are also involved in related research. They include the NICHD, the NHGRI, the NIMH, and the NIA. A multidisciplinary approach to understanding this complex disorder can allow the more rapid translation of research to patient care. The Committee urges the Director to coordinate research efforts in epilepsy among these Institutes, and to implement the NINDS research benchmarks resulting from the March 2000 conference "Curing Epilepsy: Focus on the Future." (p. 168)

Action taken or to be taken

The NINDS is committed to understanding the causes of, and developing effective therapies for, all forms of epilepsy, with the ultimate goal of finding a cure. Over the past year, NINDS, working together with the epilepsy research and advocacy communities, has continued to make progress in addressing the 17 research benchmarks, which were developed following the March 2000 White House- initiated Conference, "Curing Epilepsy: Focus on the Future." Several workshops focused on benchmark topics have been held, including "DNA Microarrays and Epilepsy" (October 2002), "Channelopathy" (November 2002), and "Imaging Markers of Epileptogenesis: New Research Directions" (April 2003). In August 2003, NINDS released a Request for Applications on "Model Validation for Antiepileptogenic and Resistant Epilepsy Therapies," which was a direct outcome of two previous workshops held on this topic in March 2001 and September 2002. In addition, the benchmark stewards held a conference call in August 2003 to review scientific progress in their respective benchmark areas. The stewards are a group of senior well-established individuals in the epilepsy community who have volunteered to be actively involved in monitoring the status of existing and planned research that advances the goals of their specific benchmark. The stewards met at the December 2003 meeting of the American Epilepsy Society, and reviewed progress and drafted a research matrix outlining research priorities for each of the benchmark areas.

The NIH Institutes involved in epilepsy research continue to explore opportunities for collaboration and cooperation in their activities. In January 2003, staff from six Institutes (NINDS, NIMH, NIA, NHGRI, the National Institute of Child Health and Human Development (NICHD) and the Fogarty International Center (FIC)) met as an inter-Institute working group to discuss epilepsy research endeavors. The meeting attendees reviewed the epilepsy research interests of the different Institutes, and discussed areas of common interest that could be explored for possible collaborative activities. As a result of this meeting, program staff from NIA joined NINDS staff in attending a national meeting on epilepsy in the elderly, while program staff from NIMH joined NINDS staff at conferences on "Living Well with Epilepsy" and on epilepsy and mood disorders. Another meeting of the working group was held in December 2003, and program staff from the National Institute of Nursing Research (NINR), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), and the Centers for Disease Control and Prevention (CDC) were invited to join the group. In addition, NINDS intramural scientists have

formed an NIH Epilepsy Special Interest Group (SIG), composed of NIH intramural research staff with an interest in epilepsy research, which will meet on a regular basis to stimulate communication and collaboration among NIH intramural scientists.

Item

Genomics– The Committee recognizes the important role that genomics and genetics plays in the progression of disease and believes that every institute has a key role to play in moving genomics to the clinical setting through the use of next generation technologies. The Committee urges the Director to continue to ensure that the institutes and centers are pursuing every available opportunity to advance this critical research. (p. 168)

Action taken or to be taken

Please refer to page OD-54 of the document for the OD response to this item regarding Genomics.

Item

Human Embryonic Stem Cell Research-- The Committee believes strongly that embryonic stem cell research offers enormous promise for the more than 100 million Americans who suffer from chronic diseases. The Committee remains concerned that the current administration policy relating to embryonic stem cell research is too limiting and is significantly slowing the pace of this research. While the administration initially stated that approximately 70 embryonic stem cell lines would be available under the President's policy, only 11 are currently available. Moreover, the Committee has heard testimony that current embryonic stem cell lines are not sufficiently genetically diverse for therapeutic uses. Also, most all of the currently available stem cell lines are contaminated with mouse feeder cells, making it uncertain whether the FDA will permit them to be used in therapeutic applications. The Committee urges the administration to expand its embryonic stem cell research policy to allow additional stem cell lines to be available for research. The Committee is also deeply concerned with the slow pace of implementation of the current policy. The Committee was informed by NIH this year that NIH anticipates spending just $17,000,000 on human embryonic stem cell research, far short of the $100,000,000 budget originally announced by the HHS Secretary. The Committee was particularly troubled to learn that the National Cancer Institute is projecting no funding for human ES cell research in fiscal year 2003. Over the past several years, the Committee has heard from multiple witnesses, including former NIH and NCI directors, about the promise of human ES cell research to better understand and treat cancer. The Committee expects to hear from NCI during the fiscal year 2005 hearings on their plan to vigorously implement a human ES agenda. (p. 168/169)

Action taken or to be taken

The NIH is fully supportive of human embryonic stem cell (hESC) research, and is promoting this area to the full extent possible under the current federal funding policies. The NIH is working to increase the number of hESC lines available to investigators. To this end, we have awarded 9 infrastructure grants to providers of hESC lines listed on the NIH Registry. These funds support the providers' efforts to expand, test, perform quality

quality assurance, freeze, store, and distribute hESC lines to researchers. As a direct result of these infrastructure grants, 12 hESC lines are now available. NIH anticipates that more lines will be available in the very near future.

Growth on mouse feeder layers will not preclude hESCs' use in clinical trials. On May 12, 2003, Food and Drug Administration (FDA) representatives met with NIH Stem Cell Task Force members to discuss whether hESCs grown on human feeder layers would be easier and safer to use than hESC grown on mouse feeder layers. As with any proposed therapy, FDA safety requirements stipulate that risks must be balanced with the potential benefit achieved by the intervention. In the case of hESCs, the FDA would like to know certain facts before the cells can be used in clinical trials: the characteristics of the stem cells, how the stem cells were derived, the properties of any feeder layer used to propagate the cells, potential contaminants introduced through the media or serum used in culture, and the presence of infectious agents transmitted from feeder layer cells to cultured hESCs. One important point made by FDA representatives was that cell lines grown on human feeder layers are not necessarily safer for clinical trials than stem cells grown on mouse feeder layers. Both mouse and human feeder layers may harbor pathogens that could be transmitted to the hESCs grown on them. There are presently therapies in clinical trials that have been developed on animal cells. Thus, if the safety and effectiveness of human ES cell lines grown on mouse feeders can be demonstrated, these cells would be a viable option for therapy.

The NIH does not have an upper limit on funds available for hESC grants, and supports as many grants as possible that receive meritorious scores in the peer review process. At the present time, the limiting factor for hESC research is not NIH's willingness to fund the grants, but a dearth of hESC grants submitted. NIH believes this dearth is due to a lack of scientists trained to work with hESCs. The NIH is addressing this problem by funding courses to train investigators to
grow and study hESCs, providing administrative supplements to funded investigators who wish to add hESC research to their projects, and providing support for investigators who wish to redirect their research focus to learn how to grow and study hESCs.

The National Cancer Institute (NCI) believes several different types of stem cells are relevant to cancer research. The Institute plans to organize a "Think Tank" on questions related to tissue-specific adult stem cells and cancer in the coming year. NCI has not received any investigator-initiated hESC grants within the past year. However, the Institute is funding characterization of genetic transcripts present in hESCs as part of its Cancer Genome Anatomy Project (CGAP.) NCI continues to review its grants portfolio and will add initiatives to attract hESC grants as they are identified.

Item

Human Tissue Supply– The Committee is encouraged by NDRI's role in these research advances and applauds the Director's expanded support for NDRI by bringing NEI, NIDDK, NIAID, NIAMS, and the Office of Rare Diseases into the multi-institute initiative. While this is promising, more needs to be done to match the demand for the use of human tissue in research. The Committee, therefore, urges the Director to increase the

increase the core support NDRI receives from NCRR, and to continue to encourage the Institute Directors to identify and implement program-specific initiatives intended to expand support for NDRI. (p. 169)

Action taken or to be taken

The level of funding to support the NDRI activity is determined after review for technical merit, usually by peer review of the NDRI proposed activities and followed by a second level of review by NCRR's National Advisory Research Resources Council. Support provided by other NIH entities for NDRI is similarly determined.

Item

Minority Health and Racial Disparities- Research advocates should be applied more expeditiously to ensure greater improvements in health outcomes across all communities of color and the general public. The Committee urges the NIH to improve, strengthen and expand its systems of information dissemination and outreach to health care providers, minority organizations, and the public. (p. 171)

Action taken or to be taken

The NCMHD focuses primarily on disseminating information through its grass-roots networks. Thus, community based outreach has been built into one of its most extensive research programs, the Centers of Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Project EXPORT), which was originally launched in FY 2002. This program is central to the NCMHD's investment strategy for addressing disparities in health status. In addition to broadening NIH's commitment to research and research training, Project EXPORT will strengthen community involvement in understanding the causes/origin of health disparities and available treatments. NCMHD also has an Office of Community Based Research and Outreach, in its Division of Research and Training Activities, for which it is in the process of hiring a new Director.

Item

Minority Institution Research Centers The Committee continues to be pleased with the NIH Director's implementation of various programs focused on developing research infrastructure at minority health professions institutions, including Research Centers at Minority Institutions, Extramural Biomedical Research Facilities, and the National Center for Minority Health and Health Disparities. Because there are a number of new competitive mechanisms for NIH to work with these research institutions, the Committee recommends that the NIH Director work closely with the Director of the National Center on Minority Health and Health Disparities to establish a program of coordination among these various mechanisms to partner with minority health professions schools to address their infrastructure needs. (Page 171)

Action taken or to be taken

The NIH Director worked with NCMHD and other IC Directors to the develop the NIH Strategic Plan and Budget to Reduce and Ultimately Eliminate Health Disparities, Fiscal Years 2002-2006. This plan is an important vehicle for collaboration and coordination used by NCMHD in its role of coordinating all of the NIH's Health Disparities Research

and will be updated annually. The NIH Director and NCMHD Director are in close communication and meet on a regular basis. The Director of NCMHD is also in close contact with the Director of NCRR on the programs mentioned above as well as other IC Directors in the coordination of other health disparities research programs.

Item

NIH/DOE Medical Technology Partnership-- The Committee expects the NIH to continue to collaborate with the Department of Energy to evaluate the technologies developed within the nuclear weapons program and other DOE programs in terms of their potential to enhance health sciences, with the goal of achieving clinical applications and improved national health care. (p. 172)

Action taken or to be taken

The NIH recognizes the potential benefits of the technologies developed within the DOE s programs at national laboratories in terms of enhancing the health sciences, achieving clinical applications, and improving national health care. To facilitate translation and application of national laboratory-developed technologies to healthcare, the NIH has continued and expanded collaborations with the DOE. Active DOE participation in the NIH Bioengineering Consortium (BECON) continues to provide lines of communication between agency program leaders, national laboratories, and NIH research institutes and centers. National laboratory staff members have participated in recent BECON symposia on team science and biosensors and have identified potential future collaborative research and training opportunities. NIH-DOE collaborations have also resulted in increased awareness and participation in NIH biomedical funding opportunities by national laboratory staff. NIH research grants for national laboratory staff through the BECON Bioengineering Research Partnership program, which encourages and supports multi-organizational research partnerships with technological and biomedical components, have more than doubled over the past two years. To enhance communication, program staff and management from the National Institute of Biomedical Imaging and Bioengineering (NIBIB) have visited and are planning future visits to DOE national laboratories to learn about technological research and development programs and to communicate biomedical opportunities.

Item

Office of Dietary Supplements-- The Committee also expects the Office of Dietary Supplements to contract with industry nonprofit associations or foundations who currently have and maintain databases of dietary supplement labels to develop, create, regularly update, maintain, and make available to government and research entities a database of all supplement labels sold in the United States. The creation of this database would allow ODS to have access for research purposes of all known supplements manufactured in the United States and to allow access by other Federal agencies for ensuring safety to consumers (through the mandatory listing of ingredients in these products on the label) who purchase supplements manufactured and/or sold in the United States. (p. 172)

Action taken or to be taken

The ODS has already begun to create two databases of dietary supplements – one for labels and one for ingredients – that are intended to support research. It is unclear how the database proposed in the Senate Report language would differ from the database of labels that ODS has already developed in partnership with the CDC National Center for Health Statistics. ODS has regularly engaged in collaborations with stakeholders in dietary supplement research, including industry, and welcomes the opportunity to discuss the intended goal of this proposal in more detail.

Item

Office of Rare Diseases -- The Office of Rare Diseases [ORD] plays an important role in bringing funding and attention to rare disease research, in cooperation with the institutes and centers. The Committee is concerned, however, that ORD has not directed sufficient attention to rare liver diseases such as autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cirrhosis. The Committee urges ORD to work closely with NIDDK to develop an appropriate response to address these significant diseases and to work toward a comprehensive research agenda. (p. 172)

Action taken or to be taken

The Office of Rare Diseases (ORD) works very closely with NIH institutes and centers and offices including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute (NHLBI). Within the area of rare liver diseases research, ORD is cofunding with the NIDDK the Biliary Atresia Research Consortium (BARC), which contains nine pediatric liver disease centers. The aims of this consortium are to develop and test hypotheses on the cause of biliary atresia and to help define the best means of diagnosis and management of this disease.

ORD cosponsored with the National Institute of Environmental Health Sciences (NIEHS) and the NIDDK and others, a scientific conference on the emerging area of metabolic profiling and its application to the health sciences. Research scientists (molecular biologists, analytical chemists, toxicologists, clinicians, nutritional scientists and computational biologists) defined the current state of the science in metabolic profiling and its application to the health sciences. Specific emphasis was placed on the application of metabolic profiling to toxicology and risk reduction.

The conference provided a forum for identifying scientific initiatives needed to stimulate metabolic profiling research and to develop partnerships between academia, government, and industry with the hope of better treatments of metabolic and digestive diseases.

With regard to rare liver diseases, the NIDDK is committed to advancing knowledge of the autoimmune liver disease that encompasses three major diseases, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH). All three diseases are uncommon (each affecting 10-50 persons/100,000 population), but they are all capable of leading to end-stage liver disease, liver failure, and the need for liver transplantation. The NIDDK is funding large multi center trials of therapy both for PBC and PSC in the Clinical Trials Program of the Division of Digestive Diseases and Nutrition. In addition, both NIDDK and NIAID fund several basic research projects (R01s) in PBC, PSC and autoimmune hepatitis which focus on underlying causes of these diseases. In the past year, the NIDDK has made efforts to stimulate

efforts to stimulate research in these important diseases. On June 16, 2003, the Digestive Disease Interagency Coordinating Committee, which the NIDDK chairs, held a half-day workshop on primary biliary cirrhosis, which focused on current status of understanding of this disease and the challenges for future research. In a similar manner, the NIDDK, in conjunction with the American Association for the Study of Liver Diseases (AASLD), has proposed a workshop on autoimmune hepatitis and needs for future research for November 2004. Importantly, autoimmune liver disease is one of the 12 targeted areas in the "Action Plan for Liver Disease Research" that is being developed by Liver Subcommittee of the Digestive Disease Interagency Coordinating Committee, which includes members of all NIH Institutes, Centers and Offices that fund liver disease-related research. A newly-formed NIDDK Liver Disease Branch is helping to spearhead this planning effort, in which the ORD will be asked to participate.

In February 2003, several NIH components cosponsored an RFA to establish a Rare Disease Clinical Research Network. This solicitation resulted in the funding of seven Rare Disease Clinical Research Centers, one of which was co-funded by the NIDDK for urea cycle disorders many of which have a significant liver disease component.

Item

Orphan Diseases – The Committee applauds the Office of Rare Diseases for its efforts to support the translation of basic research findings into improved treatments for orphan diseases. The Committee urges the Office to increase its support for demonstration or pilot projects aimed at the development of interventions for orphan diseases, including cystic fibrosis. (p. 172)

Action taken or to be taken

On September 28, 2003, the ORD and NIH institutes and centers funded the Rare Diseases Clinical Research Network in response to the Rare Diseases Act of 2002, P.L. 107-280. The purpose of the network is to facilitate clinical research in rare diseases through a collaborative approach including pilot and demonstration projects. The NIH funded seven rare diseases clinical research centers and one data center. Each center provides components required of the total network including a clinical research trials program designed to test novel therapies, develop diagnostic tests, and evaluate outcome measures. In the Rare Lung Diseases consortium,

ongoing clinical, basic, and translational studies at the participating centers have already provided insights into molecular mechanisms underlying general lung function and defense in health and disease.

Regarding cystic fibrosis (CF) directly, in 2003, ORD cosponsored a scientific conference on CF with the National Heart, Lung, and Blood Institute (NHLBI.) Scientists evaluated the current state of knowledge of macro-molecular interactions that control ion transport processes in CF and developed recommendations for future research. The conference is expected to foster the development of new basic and clinical research directions and new scientific collaborations.

Also, the recently published, cosponsored program announcement by ORD with the NHLBI for pilot studies, demonstration projects, and exploratory research studies in rare heart, lung, and blood diseases could include rare lung diseases such as CF. Awards will allow investigators with

with novel ideas to obtain research support without the need for large amounts of preliminary data that
often serve as a barrier to entry into the NIH grants system. It is anticipated that these efforts will ultimately result in an increased pipeline of therapeutic approaches to treatment and prevention of a wide range of rare heart, lung, and blood diseases.

In addition, the Office of Rare Diseases is in the process of convening a trans-NIH rare diseases working group which should provide an additional means of collaboration in rare/orphan diseases research including pilot and demonstration projects and focusing on rare diseases including CF.

The NIDDK will sponsor a workshop in May 2004 on protein misfolding and misprocessing in disease. The objective of this workshop is to stimulate research that will translate basic cell biology, biochemistry and biophysics findings about protein structure and assembly into potential
therapies for monogenic disorders that are within the mission of NIDDK. This workshop has significance for cystic fibrosis, alpha-1 antitrypsin deficiency, and several other rare diseases in which both the NIDDK and the ORD have a shared research interest.

Item

Parkinson's Disease -- The Committee is aware that the Parkinson's Disease Research Agenda developed by NIH in 2000 included professional judgment funding projections that totaled an additional $1,000,000,000 over 5 years to achieve a cure. The Committee strongly urges the NIH to come as close as possible to fulfilling that Agenda while maintaining the standards of peer review. . . .The Committee commends the Director, NIH, for stating his commitment to develop and implement a thorough plan for Parkinson's research, and for the initial steps taken. However, the NIH has failed to devote the resources necessary to implement it and has failed to date to fill a key leadership position, Director of NINDS. The Committee strongly urges the NIH to devote additional resources to Parkinson's research, as recommended by the Research Agenda, using all available mechanisms, including RFAs, further support of initiatives such as those begun at NINDS and NIEHS, and the Genome Institute's proteomics initiative, among others. (p. 173)

Action taken or to be taken

The generous appropriations made to the NIH over the past several years have enabled NINDS, NIEHS and other Institutes and Centers (ICs) to accelerate and expand Parkinson's disease (PD) research, while also ensuring that hundreds of other important areas of scientific opportunity and public health impact are also addressed. To this end, NIH-supported researchers continue to explore all avenues of research promise that were identified in the original PD Research Agenda, novel areas of research that have emerged since the Agenda's development, and roadblocks to progress contained in the PD Matrix. In addition, NIH scientific program managers, working with numerous external advisors from the research community, continue to develop grant solicitations and other program measures that are expediting PD research. Together, these efforts are contributing to significant scientific achievements in this field, and the NIH is committed to providing strong support for the continuation of this work.

Specific recent actions taken by NIH ICs to address the PD Agenda and Matrix include the release of a Program Announcement in October 2002, by NINDS and NIEHS, to encourage current and prospective Udall Center investigators to submit applications for support. The NINDS, along with NIEHS, is also planning the development of a centralized PD Data Organizing Center that will collect clinical data across Udall and other PD research centers, make data collection more consistent, and ensure that these data are widely available. Participation by both of these Institutes will help to maximize contributions and access to this resource. The NINDS is also making competitive supplements available to Udall Centers, in order to aid these researchers in expanding their clinical research programs. In addition, NIEHS is pursuing opportunities to strengthen its Centers for PD Environmental Research Program, established in FY 2002, by encouraging development of cross-Center research projects and shared core facilities and resources. The NHGRI has also developed a collaboration with researchers at the National Institute of Mental Health (NIMH) to examine the proteomics of mitochondrial involvement in PD. These examples provide only a small snapshot of the implementation activities underway across the NIH; a complete report on the implementation of the PD Research Agenda and Matrix will be provided to the Committee by April 2004, as requested.

A permanent Director of the NINDS was appointed effective September 1, 2003. The new Director is deeply committed to continued support of the PD Agenda and its implementation, including the fulfillment of the specific goals identified in the PD Matrix.

Item

Practice-Based Clinical Research Networks– Clinical research is more important now than ever before to translate advances in basic science into better diagnosis, prevention, treatment, and cure of disease; and to provide high-quality evidence of diagnosis and treatment effectiveness to fully integrate into daily practice decisions. Placing clinical studies at the community practice level will ensure adequate representation of patients from all age, sex, and cultural groups in clinical studies, and will also increase the number of practicing clinicians who are trained to undertake clinical research. A model for such networks was established by the Agency for Healthcare

Research and Quality [AHRQ]. The Committee urges the Director of the National Institutes of Health to adopt the AHRQ model networks to include specialty practitioners who care for the most common health problems of the American people. (p.173)

Action taken or to be taken

Please refer to page OD-50 of the document for the OD response to this item regarding Practice-Base Clinical Research Networks.

Item

Scleroderma - The Committee strongly supports the development of new research initiatives to support interdisciplinary research centers that will focus on scleroderma, a chronic, degenerative disease of collagen production, that strikes mainly women and affects multiple systems including digestive, kidney, heart, lung, and skin often leading to premature death. (p. 173)

Action taken or to be taken

Scleroderma is an autoimmune disease – a broad category of diseases in which the body's immune system attacks the body's own tissues as if they were foreign invaders – causing significant damage to target organs. In some forms of scleroderma, hard, tight skin is the extent of the disease. In other forms, however, the problem goes much deeper, affecting blood vessels and internal organs, such as heart, lungs, and kidneys.

The field of autoimmunity is currently exploding with activity and newly launched initiatives. Many NIH Institutes, including NIAMS, NIDCR, NHLBI, NIDDK, and ORWH are active members of the NIH Autoimmune Diseases Coordinating Committee (ADCC), which is led by the National Institute of Allergy and Infectious Diseases. The ADCC provides a forum for coordinating research efforts for autoimmune diseases and brings together various stakeholders including the NIH, CDC, FDA, HRSA, AHRQ, and other public and private organizations. The Committee recently developed a comprehensive research plan for autoimmune diseases, including scleroderma.

The plan is based on the premise that information learned from studying one autoimmune disease will provide valuable information for all autoimmune diseases. The plan highlights research opportunities likely to have the greatest impact on accelerating discovery of treatments or cures. Research opportunities highlighted include identifying the genetic and environmental risk factors for developing autoimmune diseases, and developing a centralized clinical research network to conduct multi-institutional clinical trials.

Approximately 80 percent of scleroderma patients will eventually develop some degree of lung involvement, which causes significant morbidity and mortality in scleroderma patients. In collaboration with the NIAMS, the National Heart, Lung, and Blood Institute (NHLBI) is supporting a multi-center clinical trial to evaluate the efficacy of oral cyclophosphamide in stabilizing or improving lung function in scleroderma patients who have active lung inflammation (alveolitis). Thirteen medical centers in the United States began enrolling patients in September 2000 and will complete enrollment within the next few months. The Steering Committee for this study is planning a second treatment trial that would evaluate other immunosuppressive drugs for improving the secondary pulmonary hypertension that causes scleroderma patients to develop heart failure. The NHLBI also supports investigator-initiated research on the molecular mechanisms that contribute to the development of pulmonary fibrosis in scleroderma patients, and funds numerous projects that address various aspects of pulmonary hypertension, myocardial and pulmonary fibrosis, and cardiac arrhythmias.

A new NIAMS funded project is using a unique sample set – lung tissue from scleroderma patients undergoing lung transplant surgery as well as lung tissue from unused donor lungs – to facilitate investigation into the cellular changes that cause the hardening of the lungs. Another new NIAMS-funded study is uncovering the cellular activities inside the blood vessels in scleroderma patients. In collaboration with the Office of Research on Women's Health, NIAMS funds research aimed at uncovering the cellular and molecular processes that contribute to the development of scleroderma.

The NIDDK participates in efforts to enhance progress in scleroderma by conducting basic research on the biology of the gastrointestinal track, as well as translational research on gastroesohageal reflux disease (GERD), one of the most common gastrointestinal manifestations of scleroderma. Similar NIDDK-supported fundamental and clinical research on renal disease may provide the foundation for developing better treatments for kidney involvement in scleroderma. The NIDCR is committed to supporting research relevant to the dental and craniofacial complications associated with scleroderma.

The NIAMS supports several projects which focus on new and innovative treatment options for patients with scleroderma including: a multi center trial to test type 1 collagen as a treatment for localized forms of scleroderma; ultraviolet phototherapy; and stem cell transplantation. In addition, behavioral scientists supported by the Institute have found that managing pain and depression may lead to improved functioning and quality of life for patients with scleroderma.

The NIAMS has taken a leadership role in generating research opportunities for scleroderma by supporting a national Scleroderma Family Registry and DNA Repository. The overall objective of this registry is to identify genes that influence susceptibility to the disease. The repository collects and stores genetic material (DNA) and blood serum from scleroderma patients and their families and serves as a national resource to scientists studying the genes associated with scleroderma. The NIAMS facilitates the transfer of basic research findings into clinical practice by supporting large-scale centers of research. For example, NIAMS supports two specialized centers of research (SCORS) in scleroderma – one at the University of Texas Health Science Center and one at the University of Tennessee. These SCORS focus only on scleroderma, and they serve as a national resource for researchers studying scleroderma. The NIAMS also supports a new multidisciplinary clinical research center with a special focus on lupus and scleroderma in African Americans. In the area of childhood rheumatic diseases, the NIAMS supports a multidisciplinary clinical research center focused on juvenile scleroderma and other pediatric rheumatic diseases.

Item

Skeletal Diseases - Given that skeletal diseases can lead to or be linked to other diseases such as depression and cancer, the Committee calls for the expansion of trans-NIH studies investigating these linkages. (p. 173)

Action taken or to be taken

Bone metastases are common in a number of cancers, and they contribute heavily to morbidity and mortality, most prominently in cancers of the prostate and breast, and in multiple myeloma. However, current understanding of the molecular underpinnings of bone metastasis is very limited. Recognizing this gap, the NIAMS joined with the National Cancer Institute (NCI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in the spring of 2002 to issue a solicitation entitled “Molecular Interactions Between Tumor Cells and Bone.” In response to this initiative, the NIAMS funded two projects to enhance our understanding of the processes of bone resorption (breakdown) and bone formation, and the mechanisms of their regulation in bone metastases. The first project will use a mouse model to define the mechanism by which osteopontin, a protein implicated in distant metastasis in breast cancer, contributes to the

the pathogenesis of bone and non-bone metastases. A better understanding of the molecular mechanism that regulates osteopontin production in breast cancer cells in bone could point the way to new therapeutic targets. The second project will bring together experts in cancer biology, bone biology, and imaging chemistry to explore the role of MMP-9, an enzyme able to digest certain kinds of tissues, in the breakdown of bone that is associated with breast cancer and neuroblastoma, the third most common form of cancer in children. Scientists will also develop new techniques to quantify the amount of bone destruction that occurs during the bone invasion that is characteristic of such metastases. The NCI funded eight projects in response to this solicitation. These new studies are all directed at either identifying or characterizing the various biological factors that the tumor cells produce that give them the ability to metastasize to the bone. Their research is directed at understanding the basic biology of the molecular events that account for homing of tumor cells to the bone. This will allow the generation of novel therapeutic reagents that will specifically attack these critical traits that the tumors acquire in order to permit bone metastases.

NIAMS-supported researchers are also examining the linkage between Paget's disease of bone and osteosarcoma. Osteosarcoma is a cancer that originates in bone, in contrast to skeletal metastases of tumors that arise elsewhere in the body, and is much more common in people with Paget's disease than in the general population. Studies suggest that similar genetic mechanisms may underlie both Paget's disease and osteosarcoma, possibly leading to therapeutic advances in both skeletal disease and cancer.

At the National Institute of Mental Health (NIMH), scientists in the Division of Intramural Programs have found that depression is a major, commonly unrecognized risk factor for osteoporosis, similar to established risk factors such as smoking or family history. Low bone mineral density is more frequently found in both men and women with depression than in the general population, and it is one of the most important risk factors for fractures. The reasons for bone loss observed in people with major depression are poorly understood, though various endocrine factors are thought to play a role. Questions about the causal linkage and whether the bone loss occurs only when a patient is actively depressed need to be determined. In elderly people, use of certain antidepressants and sedatives contributes to a greater incidence of falls and fractures.

Depression is also a risk factor for poor health outcomes among arthritis patients. A recently published study conducted in a large and diverse population of older adults with arthritis (mostly osteoarthritis) and comorbid depression found that benefits of improved depression care extended beyond reduction in depressive symptoms and included decreased pain, as well as improved functional status and quality of life. Interventions consisted of antidepressant medications and/or psychotherapy sessions.

To better understand these comorbidities, NIMH encourages epidemiological studies on frequency and distribution patterns of skeletal disease and depression across gender, racial/ethnic minority groups, and the lifespan. Studies of biological, behavioral, and psycho social risk and

protective processes to clarify which processes have the greatest relative influence on the development of these conditions is also encouraged to find factors that can potentially be modified through intervention.

NIMH also has recently released a Request for Applications "Research On Interventions For Anorexia Nervosa." Anorexia Nervosa is a rare, chronic, extremely serious and life threatening disorder. It often co-exists with other forms of psychopathology including depression, anxiety disorders, personality disorders and substance-use disorders and has serious medical co-morbidity with osteopenia and osteoporosis, as well as with cardiovascular complications, fluid and electrolyte changes and disruption in immune functioning. Despite its gravity, very little is known about the effective treatment, and ultimately, the prevention of Anorexia Nervosa. This solicitation will set up a collaborative network to address the challenges of studying this disorder and research results regarding bone loss may have implications for people with other mental illnesses.

Item

Temporomandibular joint disorders [TMJ]- The May 2003 report to Congress on Temporomandibular Joint Disorders explains that many Institutes, Centers, and Offices at NIH support research that, although not necessarily directed toward TMJ disorders, relates to this complex set of conditions. But while the research initiatives continue to grow, they lack sufficient integration, the report concludes. The Committee agrees with this finding. The multifaceted nature of TMJ disorders requires an approach that coordinates the work of the many interested parties at NIH. Unfortunately, the Temporomandibular Joint Diseases Interagency Working Group, the creation of which was first requested in fiscal year 1998 report language from Congress, has not yet succeeded in uniting NIH researchers behind a common vision for addressing TMJ disorders. While many of the individual TMJ research initiatives launched or planned by the NIH over the past several years are commendable, there is no clear plan to insure that they are the most appropriate initiatives to pursue, that they do not duplicate research that is already being supported, or that they will actually be implemented in a timely manner. For example, the May 2003 report to Congress states that "[the NIDCR in conjunction with the ORWH has begun to work with patient advocacy groups and professional organizations to develop a workshop on stigmatization of the TMJ disorders." This is the exact same language used in the May 2002 report to Congress, and there is still no date for the workshop. Because of these concerns, the Committee strongly urges the Director to oversee the development of a TMJ research agenda that would guide further research planning at the NIH, as well as the entire scientific community. Such an effort can draw upon the TMJ research recommendations from recent conferences and should include input from, at a minimum, all of the Institutes, Centers, and Offices that support research that could be directed toward TMJ disorders, as well as the TMJ Association. The Committee expects this agenda to include specific short- and long-term goals and the designation of "primary leads" to carry out those goals. (p. 174)

Action taken or to be taken

The May 2003 report to Congress described the activities of Temporomandibular Muscle and Joint Disorders Interagency Working Group (TMJDIWG). The report detailed recent scientific activities, including a number of workshops and conferences, supported by a number of

organizations within NIH. The TMJDIWG was active during the past year (FY 2003), and with input from many components of NIH, has developed a listing of research needs and relevant research opportunities.

The Director, NIH has instructed the TMJDIWG to carry out, with input from the relevant NIH Institutes, Centers, and Offices, the development of a trans-NIH research agenda on TMJ disorders (TMJD). In an effort to insure a comprehensive, broadly based, and unbiased scientific perspective, this activity will culminate in a panel review by non-NIH experts of:

- The current research portfolio;
- Current and planned research initiatives;
- Research needs and opportunities
- Short- and long-term research goals

In the process of developing a workshop for stigmatization of TMJD, it was noted that NIH held a conference in September 2001 on stigmatization. "The International Conference on Stigma and Global Health: Developing a Research Agenda" broadly addressed the societal stigmatization of some communicable and disfiguring conditions but did not directly address TMJD. Nevertheless, the TMJDIWG reviewed the proceedings of the conference, and after determining the extent of trans-NIH involvement and interest, refined the concept that will now form the basis for the forthcoming TMJD-related workshop. As a result, the workshop will be formed to address an issue that:

- Is other than what is traditionally referred to as "stigmatization";
- May be linked more to the difficulty faced by health care providers in diagnosing the disease and developing a straightforward treatment plan, rather than to societal stigmatization;
- Is associated with a broad range of diseases and conditions including TMJD, chronic fatigue, post-traumatic stress disorder, Sjogren's syndrome, irritable bowel syndrome, and other multi-faceted conditions; and
- Appears to derive from the complexity of such diseases and the co-morbidities that exist with them.

Accordingly, the Office of Behavioral and Social Science Research, OD, NIH, with input from several ICs and patient advocacy groups, has assumed the lead for development of this workshop.

Item

Translational Research Initiative - The Committee in the past has noted that while research supported by NIH has produced a wealth of knowledge about the fundamentals of human health and disease, the accumulation of scientific knowledge for its own sake is of little value unless it finds its way to hospitals and physicians, where it can be put to use in finding treatments, cures and prevention strategies for patients. Therefore, the Committee urges the Director to devote a significant amount of resources for translational and clinical research designed to develop and deliver new treatments and cures with scientific and therapeutic promise to patients with serious illnesses. (p. 174)

Action taken or to be taken

One of three major themes of the NIH Roadmap Initiative, which was launched in FY 2003, focuses on re-engineering the clinical research enterprise. Within the clinical research area, seven activities are targeted for support in FY2004 through the NIH Director's Discretionary Fund, many of which should enhance the capacity by which investigators can translate promising results from laboratory research into new diagnostic, preventive and therapeutic approaches to be tested in human subjects. Currently being designed are new training programs to build cadres of translational scientists, better clinical informatics tools to manage and analyze clinical data, approaches to harmonize clinical regulatory processes to standardize reporting requirements, and enabling technologies to improve the assessment of clinical outcomes. Plans are also underway to create translational research core service centers for manufacture and testing of new small molecules and biologicals, and to establish regional translational research centers to provide infrastructure, training, and shared research services for investigators. It is estimated that $37.60 million will be attributed to these clinical research enterprise activities in FY 2004.

Item

Young Investigators and Clinical Scientists - The Committee understands that there is an urgent need for more young investigators and clinical scientists, and therefore urges NIH to establish a trans-NIH initiative to allocate more funds for training and transitional grants and debt repayment programs, and revise eligibility guidelines, funding levels and scope to further their effectiveness. (p. 175)

Action taken or to be taken

Director's Initiative on Clinical Research

The NIH appreciates the Committee's interest in this critical area. As you may know, the NIH launched a the Director's initiative on clinical research in 1998 and since then has issued a total of 805 Mentored Patient-Oriented Research Career Development Awards (K23) to attract and train young clinical scientists. The NIH also issued 297 Mid-career Investigator Awards in Patient-Oriented Research (K24) to provide support to individuals who are in a position to enhance the clinical research capacity of their institutions and to provide mentoring support to young, developing clinical scientists. The National Center for Research Resources issued a trans-NIH, institutional career development award, The Mentored Clinical Research Scholar Program Award (K12) to offer new, interdisciplinary research fellowships for young clinicians. Many of the NIH Institutes use an award called the Career Transition Award (K22) that permits young scientists nearing the completion of their research training to apply for career development and research support that can be activated at the time of appointment to a tenure-track position. These awards make the recipients very attractive candidates for new faculty positions and have been popular vehicles for both clinical and basic scientists eager to move to independence.

Finally, the NIH encouraged improvement in the quality of instruction in clinical research by issuing the Clinical Research Curriculum Development Award (K30). The NIH has

made 59 K30 awards.

NIH Extramural Loan Repayment Programs

The NIH Extramural Loan Repayment Programs (LRPs) are used to recruit and retain highly qualified physicians, dentists, and other health professionals with doctoral-level degrees to biomedical and behavioral research careers by providing educational loan repayment to support their pursuit of biomedical and behavioral research careers in clinical research, pediatric research, health disparities research, and contraception and infertility research. The Extramural LRPs can repay up to $35,000 per year of qualified educational loan debt. The Programs provide coverage for Federal and state tax liabilities.

As mandated by statute, participants must sign a contract agreeing to conduct qualified research activities for a minimum of 2 years. Participants may competitively apply for additional 1- or 2-year renewal contracts to receive additional loan repayment benefits.

In Fiscal Year 2002, the aggregate funding level was $35.764 million, with a total of 727 awards. The Fiscal Year 2002 funding levels for each of the five Extramural LRPs were:

Clinical Research LRP (the first year implemented) funding level was $19.984 million, with a total of 393 awards;

- Pediatric Research LRP (the first year implemented) funding level was $7.961 million, with a total of 168 awards;
- Contraception and Infertility Research LRP funding level was $.759 million, with a total of 13 awards;
- Clinical Research LRP for Individuals from Disadvantaged Backgrounds funding level was $2.020 million, with a total of 41 awards;
- Health Disparities Research LRP funding level was $5.040 million, with a total of 112 awards.

To promote the fullest possible participation in the Extramural Loan Repayment Programs, the eligibility criteria were expanded in Fiscal Year 2003 to include qualifying research supported not only by the NIH, but by non-profit institutions and academic facilities. For Fiscal Year 2003, the aggregate funding level increased to $62.864 million, with a total of 1193 awards. The Fiscal Year 2003 funding levels for each of the five Extramural LRPs were:

- Clinical Research LRP funding level was $38.233 million, with a total of 727 awards;
- Pediatric Research LRP funding level was $15.330 million, with a total of 299 awards;
- Contraception and Infertility Research LRP funding level was $.715 million,

million, with a total of
13 awards;

- Clinical Research LRP for Individuals from Disadvantaged Backgrounds funding level was
  $2.131 million, with a total of 33 awards;

- Health Disparities Research LRP funding level was $6.455 million, with a total of 121
  awards.

Director's Roadmap Initiatives

In FY 2004, the NIH Director launched the NIH Roadmap to accelerate and strengthen medical research (see http://nihroadmap.nih.gov/). One very important program has been developed to re-engineer the clinical research enterprise: The Multidisciplinary Clinical Research Career Development Program (K12) was developed to train predoctoral and postdoctoral candidates in research settings that are both interdisciplinary and collaborative. The emphasis will be on new strategies and curricula with training opportunities that span a variety of disease areas; a broad range of clinical disciplines, including medicine, nursing, dentistry, pharmacy and other allied health professions; and a wide array of research areas, including biostatistics, behavioral medicine, clinical pharmacology and epidemiology. Other, training and career development initiatives issued under Roadmap address similar issues and will strengthen collaboration between disciplines and enhance the overall capacity of the medical research enterprise.

Conclusion

The NIH recognizes the continuing need for young investigators and clinical scientists, and supports using loan repayment to encourage individuals to consider research early in their careers. Indeed, the Loan Repayment Programs have already proven attractive to young investigators. In Fiscal Year 2002, 43 percent of LRP recipients were within five years of receiving their highest doctoral-level degree, and in Fiscal Year 2003 this increased to 56 percent of the total cohort of LRP recipients. In Fiscal Year 2004 the NIH expects to fund approximately the same number of awards at the same funding levels, and will continue to aggressively recruit young physicians and scientists to research careers to ensure that the Loan Repayment Programs are part of our nation's effort to ensure a solid foundation of research professionals for the next generation.

FY 2004 Conference Committee Report Language (C.Rpt. 108-401

Item

Niemann-Pick Disease Type C — The Committee encourages the Office of Rare Diseases to work in association with NINDS in studying Niemann-Pick disease Type C (NP Type C), a rare metabolic disorder in which harmful quantities of cholesterol and other fatty substances accumulate in the spleen, liver, lungs, bone marrow, and most often in the brain. (p.776)

Action taken or to be taken

The Office of Rare Diseases (ORD) works with NIH Institutes and Centers in coordinating and/or supporting research activities on rare diseases, including Niemann-Pick disease Type C (NP Type C). The National Institute of Neurological Disorders and Stroke (NINDS), as well as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute on Aging (NIA), the National Center for Research Resources (NCRR), and the National Institute of General Medical Sciences (NIGMS) collaborate in this effort to support research on Niemann-Pick disease Type C.

In FY 2003, the ORD and the Ara Parseghian Medical Research Foundation through the Human Genome Research Institute cosponsored an international scientific conference on NP Type C. The purpose of the conference was for researchers to exchange ideas, discuss new advances in genetic research, stimulate the research of young scientists, and foster future collaborations.

Investigators at NINDS previously identified genes that, when defective, contribute to Niemann-Pick disease. The NINDS is funding research aimed at isolating mutations in these genes and determining how gene defects lead to this disease. The NINDS is also funding a number of studies that focus on understanding the causes of NP Type C with the goal of developing effective treatments. NINDS-funded investigators are studying the cellular function of the proteins implicated in the disorder, the underlying mechanisms responsible for the defective transport of cholesterol, and the causes of neuronal cell death and neurodegeneration. The NINDS also funds research to develop strategies to treat genetic neurodegenerative diseases, including using growth factors to protect neurons from degeneration and developing viral-mediated approaches to reverse the neurological damage observed in NP Type C.

Studies funded by other Institutes and Centers focus on a number of NP Type C related research issues. The NIDDK funds studies to understand the defect in cholesterol trafficking in NP Type C. Several investigators have identified molecules that partially correct this defect in cultured cells. These molecules could have implications for the treatment of NP Type C. The NHLBI is funding a number of animal and in vitro studies showing that the NPC mutation interferes with lipid metabolism, cholesterol homeostasis, and intracellular cholesterol trafficking. Although these dysfunctions cause severe damage to the nervous system, bone marrow, and other tissues and organs in patients with Niemann-Pick Disease, they also appear to catalyze reactions that may stabilize atherosclerotic plaques against rupture and may thereby protect adults who carry the NPC mutation from cardiovascular events such as heart attack, angina, and stroke.

The ORD, the NINDS and other Institutes and Centers will work collaboratively to further advance the understanding and treatment of NP Type C. ORD is in the process of convening a trans-NIH rare diseases working group which should provide an additional means of coordination and collaboration in rare diseases research including Niemann-Pick disease Type C.

Item

Research on human subjects – The conferees urge NIH to support the efforts of universities, medical schools, scientific societies and other groups that are working to develop and implement a system for voluntary, peer-driven accreditation of organizations throughout the country which are engaged in research involving human subjects. (p. 776)

Action taken or to be taken

The National Bioethics Advisory Commission, established in 1995, issued a number of reports making recommendations regarding human subjects protections. One report described weaknesses in the system designed to oversee protection of human subjects in research and suggested three changes: 1) a general shift of requirements away from procedure and toward education; 2) a more strategic use of the Initial Review Board (IRB) review; and 3) a more strategic use of monitoring, including accreditation. Concurrently, other entities, such as the Department of Health and Human Services' National Human Research Protection Advisory Committee and the Institute of Medicine (IOM) of the National Academies, were addressing similar issues. In particular, an IOM committee to "Assess the System for Protecting Human Research Subjects" drafted a report looking at accreditation standards for IRBs, and subsequently held a public forum where it heard witnesses comment on draft accreditation standards devised by Public Responsibility in Medicine and Research (PRIM&R), a group that has been involved with educating IRB members and others about the human subject protection system. Finally, a major impetus for independent accreditation derived from NIH efforts in the late 1990s to reduce
regulatory burdens on the research grantee community. As part of that effort, the NIH identified the development of an independent accreditation system as an integral component in the effort to reduce regulatory burdens related to human subjects protections.

Subsequently, the Association of American Medical Colleges organized the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP), which is affiliated with several organizations, including PRIM&R. AAHRPP is a non-profit entity, outside the government, that functions as an accreditation body to monitor and evaluate human protection programs at major educational institutions. In addition, the National Commission for Quality Assurance partnered with the Joint Commission on Accreditation of Healthcare Organizations to form the Partnership for Human Research Protection, Inc. (PHRP). Both AAHRPP and PHRP have consistent standards, but focus on different types of IRBs. For example, the PHRP program may be more accommodating to the needs of an independent IRB than would the AAHRPP program.

Finally, the NIH recently established a Human Subjects Research Enhancements Program to foster the development of institutional enhancements to human subjects protections and IRB functions. In a letter to National Institutes of Health Acting Director Ruth Kirschstein, M.D., AAHRPP expressed its appreciation for the creation of that program, concluding that the program "…will serve institutions well; as their oversight activities are enhanced, the public and research participants will be reassured that we place their welfare and dignity first." The NIH will continue to provide leadership and

strong support for the concept of independent accreditation.

Item

Effect of B vitamins– The conferees encourage the Office of Dietary Supplements and NCCAM to review and consider funding research to elucidate the mechanisms of action of the B vitamins and antioxidant phytochemicals in berries so that work in animal models can be extended to human studies. Research with animals has shown that diets containing berry fruits (such as blueberries) as well as B vitamins can forestall and perhaps reverse many of the neurological changes that are associated with age-related neurodegenerative conditions such as Parkinson's and Alzheimer's disease. (p. 776/777)

Action taken or to be taken

The Office of Dietary Supplements (ODS) and the National Center for Complementary and Alternative Medicine (NCCAM), in consultation with other NIH Institutes and Centers (ICs), reviewed the NIH research portfolio that relates to mechanisms of action of B vitamins and antioxidant phytochemicals in berries. Botanical and other dietary supplements, including vitamins, are among the most popular complementary and alternative medicine therapies. National surveys indicate that more than half of adults in the U.S. take some form of dietary supplement to prevent or treat disease. Despite promising preliminary research results and widespread use of botanical ingredients– whether from traditional herbal medicines, like *Ginkgo biloba*, or foods, such as berries or soy–biomedical research in this area has been limited.

NIH has funded many studies related to the mechanisms of action of B vitamins. With particular reference to neurological changes, NIH (particularly the National Institute on Aging) supports both basic and mechanistic research of these constituents, including animal and human studies, along with studies of antioxidants and polyphenols from other food and supplement sources. Relevant research is also supported by the US Department of Agriculture (USDA). In addition, ODS supports several resources that can support further research in this area, including its

Evidence-Based Review Program, its Analytical Methods and Reference Materials Program, and its emerging Dietary Supplement Ingredient Database, jointly developed with USDA's Agricultural Research Service.

NCCAM supports several projects on the use of vitamins and antioxidants, including research regarding the potential of fruits and berries to prevent and treat disease. For example, urinary tract infections (UTIs) are a serious health problem affecting millions of Americans. The use of cranberry (*Vaccinium macrocarpon*) to prevent or treat UTI is common. Preliminary evidence from small controlled and non-controlled clinical trials suggests that cranberry may relieve symptoms associated with UTIs and may reduce the need for antibiotics. In addition, limited evidence has emerged about possible beneficial effects of cranberry for other medical conditions, including inhibition of certain *Haemophilus influenzae* strains–a common cause of ear infections in infants and children. However, before rigorous, large-scale basic and clinical investigations can be

conducted on a botanical, such as cranberry, it is critical that research-grade product be made available. Therefore, in FY 2002 NCCAM awarded a contract which resulted in the development and preparation of standardized, research-grade cranberry products and matching placebos to be used in NIH-supported basic and clinical cranberry research. With the availability of a well-characterized cranberry product for research, NCCAM, in collaboration with the National Institute of Dental and Craniofacial Research, the National Institute of Diabetes and Digestive and Kidney Diseases, and ODS, has awarded funding for basic and clinical research on the mechanisms of action and role of cranberry in the prevention and treatment of urinary tract infections and other conditions.

Beyond cranberry research, NIH supports many other projects related to botanical and other dietary supplements. For example, in FY 2002, NCCAM funded research to determine antioxidant components in certain tropical fruit extracts that could serve as models for potential novel therapeutic agents for the treatment of high cholesterol. In FY 2003, the National Cancer Institute funded research to explore the chemopreventive effects of black raspberry extracts. NCCAM also supported a project to detect and understand the mechanism of action and interaction among certain phytochemicals known as proanthocyanidins. Knowledge gained from this study will help define potential standards and dosages for these phytochemicals.

ODS, NCCAM and the National Institute of Environmental Health Sciences (NIEHS), along with other NIH partners, fund a series of multidisciplinary "Dietary Supplement Research Centers: Botanicals," around the country. Among the studies that are supported through this program are ones that address the molecular actions of grape-derived phytochemicals, notably proanthocyanidins, in animal models of neurodegeneration. In December 2003, ODS, NCCAM, and NIEHS issued a request for applications to renew this Centers program, with the goals to:

- promote interdisciplinary collaborative study of botanicals, particularly those found as ingredients in dietary supplements
- conduct research of high potential for being translated into practical benefits for human health.

It is entirely within the scope of applications for these new Centers to focus some of their research on berries. Following peer review, awards will be made in FY 2005 to the most meritorious applications. NIH continues to encourage submission of proposals for further research in this area, covering the range from basic to translational studies.

Item

NIH Roadmap Initiative -- The conference agreement includes language proposed by the Senate authorizing the Director of NIH to enter into agreements to carry out research in support of the NIH roadmap initiative. The House bill did not include such a provision. This provision has been included to assess the merits of this funding approach and to demonstrate whether this funding mechanism would accelerate the research agenda. The conferees direct the Director of the NIH to enter into these agreements solely on the basis of scientific merit, opportunity for medical breakthroughs and urgency of need. The conferees understand that all awards would be subject to a competitive process. The language in this Title appropriating funds for the Office of the Director of NIH includes a limitation of $7,500,000 which may be used under the authority created in this general

authority created in this general provision. (p. 809)

Action taken or to be taken

The appropriations language in the Office of the Director account and in Section 221 of the L/HHS General Provisions authorize the Director, NIH, to use up to $7.5 million of the Director's Discretionary Fund [Sec. 402 (i) of the PHS Act] in the OD account to enter into agreements other than the currently authorized transactions mechanisms such as grants, contracts, or cooperative agreements, to carry out research in support of the NIH Roadmap. The bill language also permits the Director to use the elements of peer review the Director deems appropriate for this particular mechanism, but not to be bound by all of them. The statement of managers section quoted above indicates that the awards are to be made on the basis scientific merit, opportunity for medical breakthroughs, urgency of need, and through a competitive process.

The intent of the authority is to provide an additional mechanism to the NIH Director to move quickly to initiate projects under the NIH Roadmap. It is intended as a pilot project for the agency to determine if such authority might offer an advantage to the agency in initiating certain innovative projects in a streamlined manner. The authority is intended for use to support and complement a top priority: the NIH Roadmap for Medical Research. The NIH Roadmap, which is intended to use new scientific advances to speed research and develop treatments for diseases, will be an essential component of moving research findings from the bench to the bedside at a faster rate and could have an enormous impact on the Nation's ability to improve public health.

NIH appreciates the opportunity to pilot this additional authority, and will use it consistent with the intent indicated in the conference agreement. The *FY2005 Budget* also seeks to have this authority extended into FY2005. It will otherwise be very difficult to assess its value until it has been piloted over a few years, after which an evaluation of the utility of the authority can be completed. The *Budget* also seeks to remove the $7.5 million limitation, so that the science can determine how much of the funding in the Director's Discretionary Fund being used for the NIH Roadmap should utilize this permissive authority, rather than a specified dollar limit.